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A Preliminary Report on the Use of Para-Amino Salicylic Acid in the Treatment of Pulmonary Tuberculosis

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In 1944 Lehmann,[1,2] in Sweden, first used para-amino salicylic acid to inhibit the growth of tubercle bacilli in vitro. The drug's action on the tubercle bacillus was thought probably due to an effect on the oxidation-reduction mechanism in the metabolism of the microorganism. It was shown earlier by Bernheim[3] that salicylic and benzoic acids increase the oxygen uptake on growing tubercle bacilli. The natural sequence was to find a chemical that would have the opposite effect. A large number of related compounds were studied, but the para-amino salicylic acid was found to be the most effective in suppressing the growth of tubercle bacilli. The peculiar feature is that only when the amino group is in the "para" position is there a reversal of oxygen uptake. It was later found by Sievers[4] that the drug, conveniently designated as P.A.S., inhibited the growth of tubercle bacilli, but had no effect on a large number of other pathogenic bacteria. In this respect it differed from most of the new chemotherapeutic agents.

Lehmann's work on experimental tuberculosis in guinea pigs

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elicited some toxic reactions. The animals lost appetite and failed to grow. Paradoxically, he encountered only slight toxic effect in human beings, most of which was manifest as gastro-intestinal irritation.

The first clinical report by Lehmann was encouraging, and later joint reports by Vallentin and his associates[5] throughout Sweden, as well as reports by Alin and Difs,[6] Dempsey and Logg,[7] Lemming,[8] and others, have confirmed the fact that certain forms of tuberculosis appear to respond favorably to treatment with the drug. P.A.S. has been found effective particularly to enteritis, skin sinuses, genito-urinary tuberculosis and in ulcers of the pharynx and tracheo-bronchial tree. Patients with meningitis improved in clinical symptoms, but no case has yet recovered on P.A.S. treatment alone. Carstensen and Sjolin[9] reported good results on secondary tuberculosis enteritis.

In this country, Youmans[10] first produced a suppression of the disease in vitro and, contrary to Lehmann's findings, Feldman, Karlson and Hinshaw[11] and Youmans and his associates[12] observed little unfavorable effect of the drug on animals. Of much significance was the observation by the latter group that P.A.S. inhibited the growth of six strains of human tubercle bacilli already resistant to streptomycin.

In pursuing the delay in streptomycin resistance of tubercle bacilli following P.A.S. treatment, Karlson, Pfuetze, Carr, Feldman and Hinshaw[13] reported that they were able to find only one streptomycin-resistant strain after three months treatment out of fourteen cases of tuberculosis treated on a combined regimen of P.A.S., streptomycin, and promin. Only three resistant strains were found after six months of treatment.

The Problems Involved

The problems confronting us in this study were to ascertain the extent of the toxicity of P.A.S. on human beings; to determine its effect on clinical tuberculosis; to see if it decreased the development of resistance of tubercle bacilli to streptomycin when used with streptomycin; and to find out whether it produced a favorable result after streptomycin had failed, or when streptomycin was otherwise ineffective.

Methods

Preparation and Administration of the Drug: At first the tablets of P.A.S. were given alone, but later the acid was neutralized with 0.6 gm. $NaHCO_3$ per gram of P.A.S. The salt then produced was given in a liquid preparation in a dosage of 3 grams four times daily, usually with food.

The Control Studies of Treated Patients: Prior to treatment, the following laboratory examinations were made: Complete blood count and sedimentation rate, nonprotein nitrogen, total protein, and albumin-globulin ratio, urine analysis, and sensitivity of organisms to P.A.S. and streptomycin. Blood levels of P.A.S. were routinely taken on the tenth day of treatment. Urinalysis was repeated every two weeks; complete blood count, sedimentation rate, x-ray films of the chest, and sensitivity of organisms were repeated every thirty days. X-ray films of the chest were repeated every thirty days and following the end of therapy. Protein partition was performed every three months and at the end of treatment.

X-Ray Analysis: Analysis of the x-ray changes was estimated by two unbiased observers,* who gave opinions on series of x-ray films of patients who had received P.A.S. therapy, streptomycin therapy, placebo therapy, or only rest therapy. The observers had no knowledge of the kind of treatment the patients were receiving. They first evaluated a pre-treatment plate, then compared plates taken at 30 day intervals, employing classifications: Worse; stationary; slight improvement; moderate improvement; marked improvement.

Clinical Examinations: The clinical condition of the patient was followed by personal interview and examination of each patient at two week intervals, at which time information was tabulated concerning cough, expectoration, weight, etc.

The results include work on groups of patients, most of whom have finished four months of therapy with the exception of the group investigated on fever alone. A few patients had six months' treatment.

Clinical Trial of P.A.S. on Pulmonary Tuberculosis: The number of cases treated so far, is too small to give anything but a general impression of the effectiveness of P.A.S. against pulmonary tuberculosis. There was a definite and unmistakable improvement in over half of the cases. The cases treated were of two general types —the acute "exudative," or those with recent infiltrative lesions, and cases with chronic fibro-caseous and ulcerative lesions. Almost all cases treated were far advanced, many having a prognosis of zero at the time the treatment was begun. Six fairly representative case histories and x-ray reproductions will be given to illustrate the various aspects of the study.

Cases with Pneumonic and Infiltrative Lesions: Of the acute infiltrative type there were eight cases. One died soon after the treatment was begun, and in another the drug was discontinued

*Dr. Leroy Berard, Clinician, and Dr. Flora Brown, Roentgenologist.

because of gastro-intestinal symptoms. Of the other six, one became worse, with a spread to the other side; one remained stationary; one was slightly improved; two moderately improved; and one was markedly improved. There was improvement in 50 per cent of all the cases in this group.

The first case history presented is that of the patient who showed no improvement and actually became worse for awhile. Later her condition became stationary.

Case 1: V.D., No. 61649 was a thirty-one-year-old negro housewife, married and with two children of ages thirteen years and sixteen months, respectively. The children were living and well. The patient's contact with tuberculosis was unknown.

Onset was insidious and first noted in September, 1948.

Past History was not significant.

Present Illness began with a non-productive cough in September, 1948. Soon after, the patient noticed a loss of appetite and weight. About two months later the patient began to run a fever and to have night-sweats. She lost twenty-three pounds in three months.

Physical Findings: The patient was sixty-one inches tall and weighed eighty-nine pounds. Her average weight was one hundred pounds, her best weight one hundred and twelve pounds. The cough was productive of 125 cc. of mucopurulent sputum daily, positive for tubercle bacilli. The x-ray examination revealed that the major portion of the right lung was occupied by a soft consolidation, most dense in the base. A cavity 3 cm. in diameter was seen in the second interspace, apparently localized in the apex of the right lower lobe. It was thought also that a lesion might be developing in the left lung at the level of the first interspace close to the mediastinum. The diagnosis was pulmonary tuberculosis FAB.

P.A.S. Treatment was begun January 17, 1949. The laboratory findings prior to treatment were as follows:

Blood: Red blood corpuscles, 4,630,000; white blood cells, 10,350; hemoglobin, 78 per cent; red cell sedimentation rate (Cutler method), 22 mm. in one-half hour.

Non-Protein Nitrogen: 24 mg. per cent.

Urine was negative for albumen and sugar and had a specific gravity of 1.011.

Sputum was positive for tubercle bacilli on concentration.

Progress Notes: The patient did well clinically until March 31, 1949. She had gained six pounds, her temperature decreased, her cough was less, and expectoration had diminished from 60 to 30 cc. daily. However, at that time it was noted that a new lesion had developed in the middle one-third of the left lung, extending outward from the left hilum. The x-ray film showed clearing of the exudative components of the right lung, but a cavity in the apex of the right lower lobe had increased in size. Although P.A.S. was continued, the chest findings became more pronounced; rales appeared in the left lung, and the patient developed a severe cough, with increased expectoration to 100 cc. daily.

At the present time (June, 1949) the cough has again diminished remarkably, and the chest findings in the left are minimal. There is now much clearing of the new lesion on the left and further clearing of the extensive lesion on the right.

The sputum was cultured on May 5, 1949, and found positive for tuber-

cle bacilli. The bacilli were sensitive to less than 1 microgram of streptomycin. Bacilli from a culture of February 16, 1949, were sensitive to less than 0.1 mg per cent P.A.S. The sputum culture was negative on concentration in June, 1949.

The red blood count on June 1, 1949, was 4,320,000; white blood count, 11,100; hemoglobin, 69 per cent; sedimentation rate 25 mm.

Case 2: F.F., No. 61615 was a thirty-six-year-old white male, married and having one healthy child six years old. His occupation was that of bartender. The contact is unknown.

The Onset was insidious in November, 1948.

Past History: The patient suffered a dislocation of the right hip with an osteomyelitis in 1917. He had been a heavy drinker, consuming a fifth of a gallon of liquor daily in the year prior to admission.

Present Illness: The patient had had a morning "cigarette cough" with production of 5-6 cc. of mucoid sputum daily for some years.

Physical Findings: The patient appeared chronically ill; symptoms were moderate. There were exaggerated breath sounds, and moisture and dullness in the right apical region. The sputum was positive. The x-ray inspection disclosed soft exudative consolidation scattered throughout the upper half of the right lung with numerous small irregular cavities throughout. At least one fairly large cavity was seen to fill the apex of the right lung. There was no definite involvement seen in the left lung. The liver was palpable. The diagnosis was pulmonary tuberculosis FAB.

P.A.S. Treatment was begun on January 3, 1949. The laboratory findings preceding treatment were as follows:

Blood: Red blood corpuscles, 3,990,000; white blood cells, 10,250; hemo-

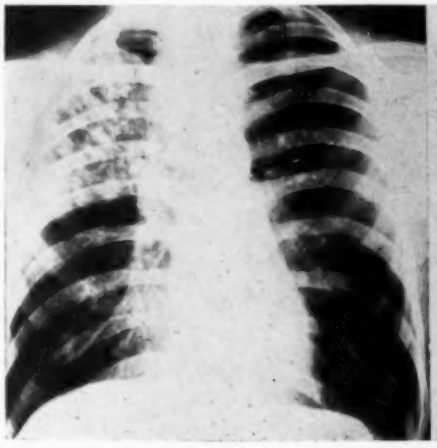


FIGURE 1

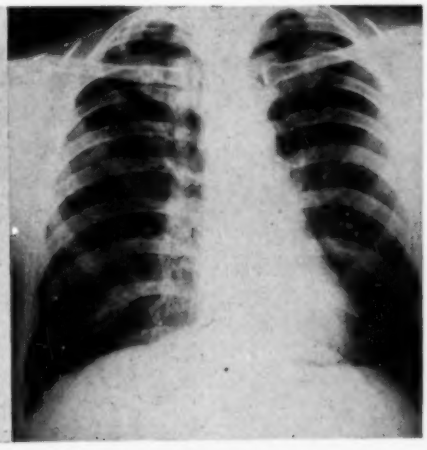


FIGURE 2

Fig. 1: Roentgenogram of Case 2 (F.F.) taken November 23, 1948, before P.A.S. was given. There was a mass of irregular infiltration in the whole right upper lobe. There were many small irregular annular shadows throughout and one large one in the apex.—*Fig. 2:* Another x-ray film taken of the same case May 28, 1949, nearly two months after the end of the treatment—much clearing of infiltration, and all the annular shadows had disappeared from view. Pneumothorax was instituted on the right on May 24, 1949. While some of the clearing may be due to bed rest and change in habits, the change noted would practically never have happened on regular treatment in the same period of time.

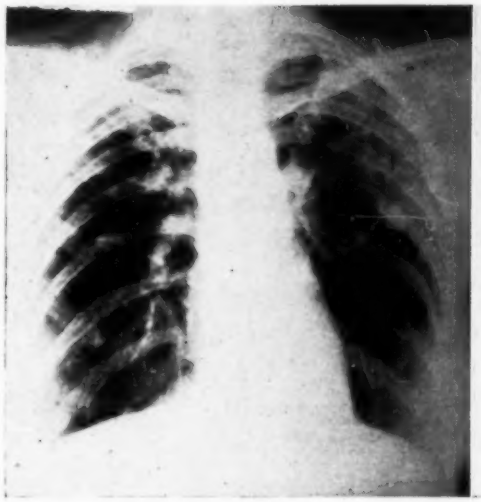


FIGURE 3

FIGURE 4

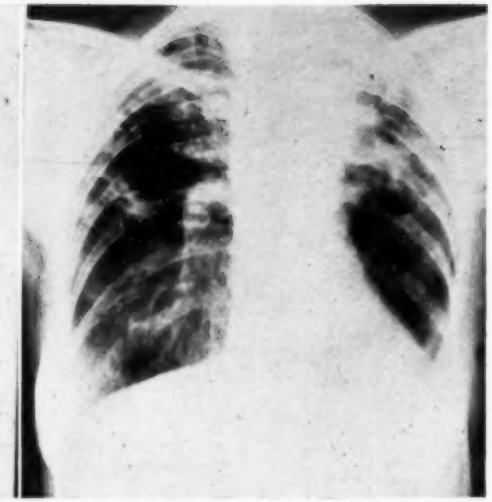


FIGURE 5

Fig. 3: Roentgenogram of D.W. taken July 15, 1939, eight years before treatment, showing extensive bilateral fibro-ulcerative disease. *Fig. 4:* Same case on May 27, 1948, twenty-three days before P.A.S. treatment was begun after eight years of progressive disease. Note the many early bilateral cavities.—*Fig. 5:* Same case on August 9, 1948, fifty-eight days after P.A.S. treatment was begun. There was a marked shrinking of all the visible cavities with slight clearing of the infiltrative lesions.

globin, 66 per cent; red cell sedimentation rate (Cutler's method), 25 mm. in one-half hour.

Non-Protein Nitrogen: 34 mg. per cent; fibrinogen, 0.74 gm. per cent; globulin, 2.80 gm.; A-G ratio, 1.49; total protein, 7.71 gm.; serum bilirubin, within normal limits; cephalin flocculation, negative.

Urine: Specific gravity, 1.012; other findings negative.

Progress Notes: The patient showed marked clinical improvement, with a gain of 23¾ pounds in weight (June 1, 1949). The temperature became normal. There was no definite change in cough or expectoration, but his general condition was good. The x-ray film showed moderate improvement in the extensive disease in the right upper lobe (Figs. 1 and 2).

The sputum remained positive on concentration. A culture done on May 9, 1949, was positive, and the bacilli were partially resistant to 1 mcg. streptomycin. Bacilli from a culture of March 4, 1949, were sensitive to less than 0.1 mg. per cent P.A.S. A right pneumothorax was initiated on May 24, 1949.

Shortly after this time, the red blood count was 4,810,000; white blood count, 12,100 hemoglobin, 85 per cent; sedimentation rate, 20 mm. (19 per cent gain). The non-protein nitrogen was 31 mg. per cent; fibrinogen, 0.57 gm. per cent; albumen, 4.38 gm.; globulin, 2.27 gm.; A-G ratio, 1.93; total protein, 7.22 gm. The urine was normal.

This second case made a marked improvement.

Of the chronic fibro-caseous and ulcerative cases, there were three categories treated. The first included seven cases treated for 120 days or more. One patient left before the treatment was finished, and one is still under treatment. Of the five remaining cases, one was worse; one was stationary; one was slightly improved; one moderately improved; and one markedly improved. Of the completed cases, 60 per cent improved.

In Case 3 there was marked improvement, but resistance of the bacillus to P.A.S. developed with a relapse of the patient's condition.

Case 3: D.W., No. 48647, was a fifty-one-year-old white female, single, and an office worker.

The Onset was catarrhal in July, 1939.

Past History: The patient has been under the care of a physician for a multitude of ailments (nose trouble, arthritis, tuberculosis, etc., from July, 1939, until 1947, when she began to cough and raise sputum.

Physical Findings: X-ray inspection revealed infiltration of both upper lung fields. The diagnosis was pulmonary tuberculosis, FAB. Routine rest treatment was recommended.

Interval Note: After some time, multiple thin-walled cavities appeared in both lungs. For at least two years prior to the institution of P.A.S., there had been a daily rise of temperature to 101.4 degrees F. The sputum was consistently positive. The patient has had vague abdominal distress, characterized by nausea, particularly when taking fruit juices. (An x-ray work-up, however, of the G.I. tract and gallbladder was negative). Over the last two years her weight has varied from 94 to 100 pounds.

P.A.S. Treatment was begun June 19, 1948, given 10 gms. daily in four divided doses. The laboratory findings before the beginning of P.A.S. therapy were as follows:

FIGURE 6

FIGURE 7

FIGURE 8

Fig. 6: Same case (D.W.) 123 days after P.A.S. treatment, with continued shrinking of cavities and clearing of infiltrative lesions.—*Fig. 7:* Same case on January 22, 1949, at the time P.A.S. treatment was stopped. The bacilli on February 8, 1949, were resistant to 100 mgs. per cent P.A.S. The clinical condition, the x-ray films (enlarging cavities) laboratory findings show deterioration of the patient's condition.—*Fig. 8:* Same case after retreatment with P.A.S., but to practically no avail.

Blood: Red blood corpuscles, 4,040,000; white blood cells, 8,600; hemoglobin, 66 per cent; red cell sedimentation rate (Cutler method), 22 mm. in one-half hour. Bacilli from a culture of September 12, 1948, were sensitive to 0.39 mgs. per cent P.A.S.

Urine: The laboratory findings were negative.

The x-ray film showed bilateral, far-advanced pulmonary tuberculosis, with multiple cavitations.

Progress Notes: Three days after the beginning of treatment, the temperature dropped to normal, with a single rise to 101 degrees F. and an occasional rise to 99 degrees F. By December 31, 1948, the patient had gained four pounds, her G.I. symptoms had subsided, and she felt better and appeared clinically improved, though there was very little change on physical examination. On x-ray inspection (November 19, 1948), a remarkable decrease in the size of the cavities was noted.

On January 17, 1949, the patient showed considerable improvement in symptomology. The x-ray film revealed marked clearing and remarkable diminution in the size of the cavities. P.A.S. was discontinued on January 24, 1949.

The sputum culture of February 8, 1949, was positive, and the bacilli were resistant to approximately 100 mg. per cent of P.A.S. All strains recovered were sensitive to less than 1 mcgm. of streptomycin.

Her clinical condition again became progressively worse; she began running a low-grade fever, and the cavities increased in size. Her sputum had increased again from about 100 cc. to nearly 300 cc. daily.

A second course of P.A.S. was started on April 4, 1949. The patient's general condition at this time is poor; she has been having slight hemorrhages for the past few weeks. The temperature rises to 99.4 degrees F., and there are probable extensive bronchial changes now present. The x-ray films do not reveal any essential changes since the beginning of the second course of P.A.S.

On June 1, 1949, the red blood count was 4,120,000; white blood cells, 6,500; hemoglobin, 70 per cent; sedimentation rate, 25 mm.

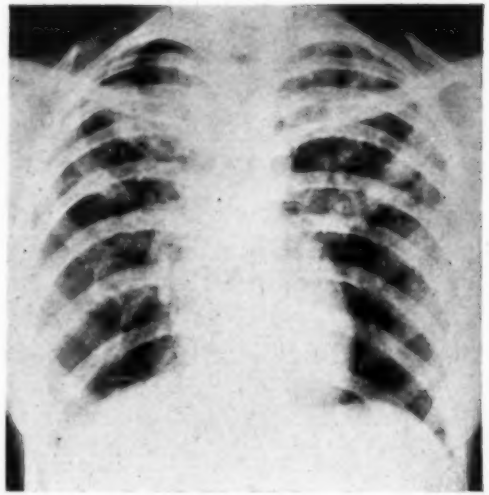
The second group consisted of thirteen cases treated with the drug. They were matched as closely as possible with thirteen similar cases, who were given a placebo instead of the drug. We were obviously not harming any of these control cases because most of them had a grave prognosis at the time of selection, and there was no other treatment indicated than bed rest.

Of the treated cases, only eight have finished ninety days of treatment. Of these, three have shown no improvement; three have shown slight improvement; while two have shown moderate improvement. The improved cases represent 62.5 per cent of those treated for ninety days.

The five remaining cases have completed sixty days; two are stationary; two slightly improved; and one moderately improved. The improved cases represent 60 per cent of the group.

Of the controls, six have had ninety days of treatment, two of these have become worse, and four others have not improved.

Of all the cases treated with P.A.S. alone, there was a rather uniform improvement in fifty to sixty per cent of the acute and



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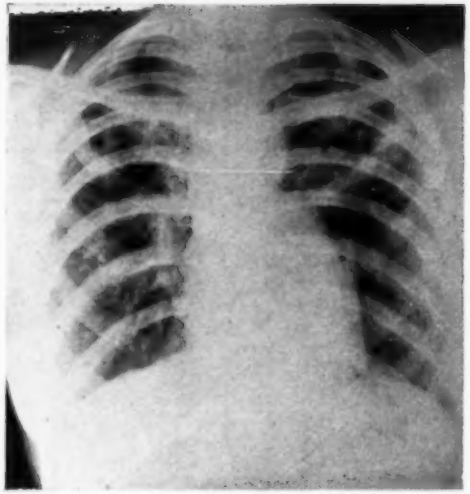

FIGURE 10

FIGURE 11

Fig. 9: Roentgenogram of Case 4 (V.S.) taken on October 2, 1947, 28 days before streptomycin treatment was given (1 gram daily for 46 days and then 0.5 gms. daily for 74 days).—*Fig. 10:* Same case on February 11, 1948. After 113 days of streptomycin treatment, with marked clearing of the infiltrative lesions.—Fig. 11: Same case on July 1, 1948, over four months after streptomycin was stopped, and 51 days before P.A.S. was begun. Note the many cavities and new infiltrations.

chronic cases selected for treatment. Some of the cases have shown a remarkable improvement, too great to ascribe to anything else but the drug, especially since the control cases have shown no corresponding improvement. It appears to us, however, that the improvement is perhaps a trifle less and somewhat slower than we have observed in corresponding cases treated with streptomycin, but there is the possibility, rare in streptomycin-treated cases, of continuing the treatment for long intervals of time and thus achieving a result approaching, or perhaps exceeding, that obtained with streptomycin.

The Effect of P.A.S. on Patients Failing to Respond to Streptomycin or Relapsing After a Temporary Improvement on Streptomycin

Fifteen cases are included in this group, but only nine are completed to date. Of the nine cases completed, two were worse, one was stationary, two slightly improved, and four markedly improved. Therefore, there were 55.6 per cent improved with 44.4 per cent markedly improved. One case (5), showing marked improvement, was given a pneumoperitoneum. It appears to us that this type of case offers a definite reason for optimism in the future use of P.A.S. In a few cases, there was an unequivocal favorable result where practically a zero prognosis had existed.

Case 4: V.S., No. 60014, was a 22-year-old white female, an office worker.

The Onset of the disease was catarrhal in June, 1947. The past history is not significant.

Present Illness: In June, 1947, the patient developed marked fatigue, cough and fever. An x-ray film taken in July, 1947, showed pulmonary tuberculosis. The patient spent one week in the Fresh Air Hospital; she was sent home and remained in bed there until admission to the Municipal Tuberculosis Sanitarium on October 1, 1947. There had been a twenty-five-pound weight loss in three months.

Physical Findings: The patient was 65½ inches in height, weighing 114½ pounds (her best weight had been 138 pounds). Her cough was moderate. She expectorated about 90 cc. of thin, whitish-yellow sputum daily. The diagnosis was bilateral pulmonary tuberculosis FAB.

Interval Note: The patient was put on bed rest, but there was no improvement. Her temperature rose to 102.0 degrees F.

Streptomycin Treatment: The patient was given 1 gm. daily for forty-six days, then 0.5 gm. daily for 74 days (from October 30, 1947, until February 28, 1948). She had shown remarkable clinical and x-ray improvement at the conclusion of the streptomycin course. She had become afebrile, gained thirteen pounds, and was asymptomatic. The streptomycin sensitivity test from a culture revealed that the bacilli were completely resistant to 100 micrograms on April 10, 1948, March 29, 1949, and May 4, 1949.

Interval Note: The clinical improvement was maintained for four months after termination of the streptomycin treatment, when symptoms began to reappear. The cough increased, and expectoration increased to about 120 cc. There was a daily elevation of temperature to

FIGURE 12

FIGURE 13

FIGURE 14

Fig. 12: Same case (V.S.) on November 27, 1948, 110 days after P.A.S. treatment with clearing and disappearance from view of most of the cavities.—*Fig. 13:* Same case on December 24, 1948, about a month later, with more clearing.—*Fig. 14:* Same case on April 30, 1949, 68 days after P.A.S. was stopped, with marked clearing and a corresponding improvement in clinical condition, including a 23-lb. gain in weight.

99.0 degrees F. The appetite became poor, and there was a weight loss of fourteen pounds in two months. The x-ray film showed extensive involvement of both lungs with fibro-caseous and ulcerative lesions; multiple cavities were seen throughout the upper two-thirds of both lungs. The disease had made a gradual progression since the completion of streptomycin treatment.

P.A.S. Treatment was begun on August 21, 1948, as 12 grams daily in four divided doses. The laboratory findings before the beginning of treatment were as follows:

Blood: Red blood corpuscles, 4,380,000; white blood cells, 13,500; hemoglobin, 65 per cent; red cell sedimentation rate (Cutler method) 24 mm. in one-half hour.

Urine: Specific gravity, 1.015; albumen, 1 gram per litre; sugar, negative.

Progress Notes: By December 31, 1948, the temperature had returned to normal except for two elevations to 99.0 degrees F. The cough and expectoration had decreased. The sputum culture was positive for tubercle bacilli in September, but negative in November. There was a weight gain of seven pounds. The patient felt better and appeared clinically improved. There were no significant changes on the x-ray.

The red blood cell count at this time was 4,300,000; the white blood cell count was 9,000; the hemoglobin was 80 per cent; and the sedimentation rate was 15 mm. in one-half hour.

On June 10, 1949, the patient, still showing clinical improvement, weighed 137½ pounds (a gain of 23 pounds since the beginning of therapy). P.A.S. treatment was stopped on February 21, 1949. At that time there was a diminution or disappearance of some of the cavities, otherwise the findings were the same as before. In general there was considerable x-ray improvement. The sputum was positive on direct smear and on culture since January 10, 1949. On May 4, 1949, the red blood count was 4,400,000; white blood cells, 9,600 hemoglobin, 79 per cent; sedimentation rate, 14 mm. The culture was resistant to 100 mcgms. of streptomycin.

Case 5: L.N., No. 59577, was a twenty-six-year-old white female, married. She did factory work until May, 1947.

The Onset was insidious early in 1946.

Past History: The patient had frequent colds. There were three spisodes of "flu," the last one year ago.

Present Illness: The first sign of trouble was a "cigarette cough" followed by irritability, fatigue and nightsweats.

Physical Findings: There was an expectoration of 5-10 cc. of clear sputum daily. The patient complained of a dull pressure over the left chest with dyspnea on moderate exertion. Her temperature was 99-100 degrees F. There had been a 22-pound loss in weight over the past 1½ years, from 116 pounds to 89 pounds. The height was 63½ inches. The pulse was 96 and the blood pressure 96/58. The x-ray findings revealed several cavities and soft infiltration involving the upper two-thirds of the left lung and a small patch of infiltration in the right mid-lung field. The diagnosis was pulmonary tuberculosis, FAB.

Interval Notes: On June 24, 1947, a pneumothorax was performed on the left side; an intrapleural pneumolysis was done on July 24, 1947, following which the patient developed fluid. Her temperature rose to 104.0 degrees F., but later subsided to 99.2 degrees F.; the expectoration

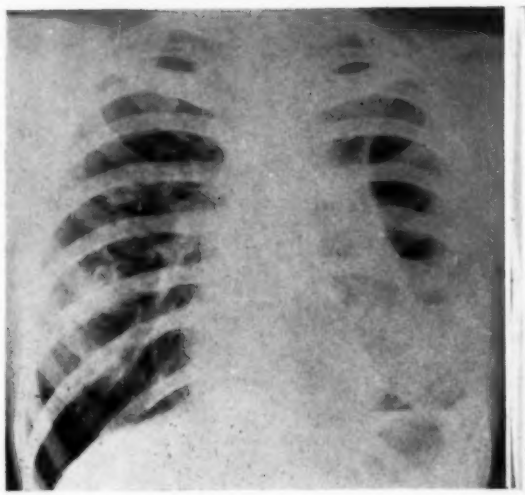

FIGURE 15

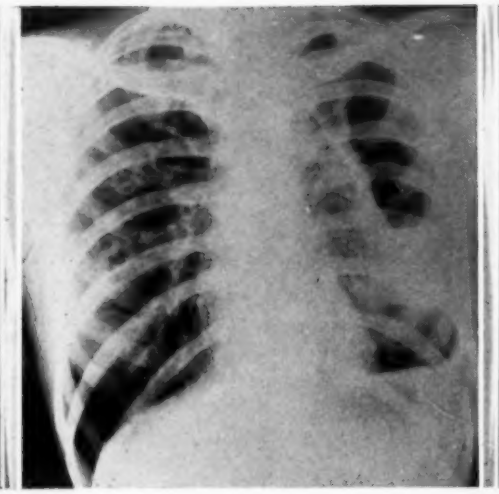

FIGURE 16

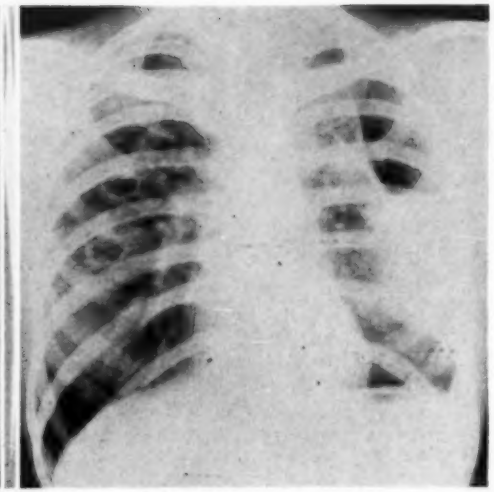

FIGURE 17

Fig. 15: Case 5 (L.N.) was a roentgenogram taken January 21, 1948, one month before streptomycin treatment was begun. There were many scattered nodules throughout both lungs, a few small cavities in the right lung, and a left empyema following an unsuccessful pneumothorax.—*Fig. 16:* Same case taken on May 21, 1948, 81 days after 0.5 gram daily dosage of streptomycin treatment was begun. There was much clearing through both lung fields.—*Fig. 17:* Same case taken July 22, 1948, 29 days after the streptomycin treatment was stopped, and 39 days before P.A.S. was begun. Note enlarging of cavities on right and beginning reexpansion of the left lung.

ceased, and the patient gained 11 pounds. The x-ray inspection, however, showed progression of the disease on the right side.

Streptomycin Treatment was begun on February 28, 1948, and continued until June 2, 1948 (94 days) in 0.5 gm. daily doses, given in two injections. At the conclusion of the streptomycin therapy, the x-ray film showed considerable clearing. The temperature was normal throughout the course. The appetite improved somewhat, but the weight remained constant. The general clinical condition seemed only slightly, if at all, improved.

Interval Note: The general condition remained unchanged, but after one month, the x-ray film revealed progression of the disease on the right side.

The red blood cell count on August 26, 1948, was 4,540,000; white blood cell, 7,500; hemoglobin, 70 per cent; sedimentation rate, 25 mm. in one-half hour.

P.A.S. Treatment was initiated on August 30, 1948, and given as 12 gm. amounts daily, divided into four doses.

Progress Notes: On December 31, 1948, the sputum was negative on culture, the temperature was normal, the expectoration was 5-10 cc. daily. There was no gain in weight. The patient stated that she felt better, and she appeared clinically improved. The x-ray film showed an increased fluid, but with a noticeable improvement in the tuberculosis lesions.

A pneumoperitoneum was instituted on April 1, 1949.

By June 10, 1949, the patient had gained five pounds, weighing 101 pounds at the end of treatment. The cough and expectoration were about the same as before treatment. The x-ray inspection revealed considerable clearing in the disease of the right lung, with closure of several cavities previously noted, and diminution in the size of the others. The left empyema showed a slight decrease in size.

The sputum has been negative on concentration since June 3, 1948, and negative on culture since August 12, 1948.

On May 4, 1949, the red blood cell count was 5,090,000; white blood cells, 10,000; and hemoglobin 83 per cent.

Combined P.A.S. and Streptomycin

Finally a group of cases were treated with combined streptomycin and P.A.S. This was done for several reasons. First, we wanted to see if we could get the additive results of the combined drugs; second, we desired to see if there was an increase over the simple summation of the results of two drugs as indicated by the experimental work of Vennesland, Ebert and Bloch;[14] and finally, we wanted to test the principle expressed by Karlson[13] and his associates as to the delay in the development of resistance of the bacilli to streptomycin as a result of treatment with P.A.S.

In this group there were nine cases, two of which had received previous courses of streptomycin, and two of which have not yet finished treatment. The two who had received previous treatment both improved, one slightly and one moderately. Of five cases completed, all showed improvement. One was slightly improved; two were moderately improved; and two were markedly improved.

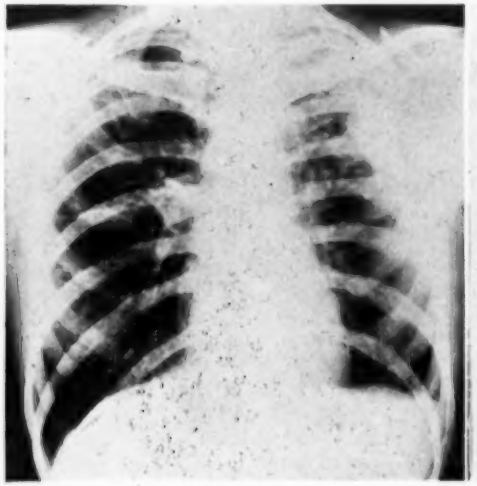

FIGURE 18

FIGURE 19

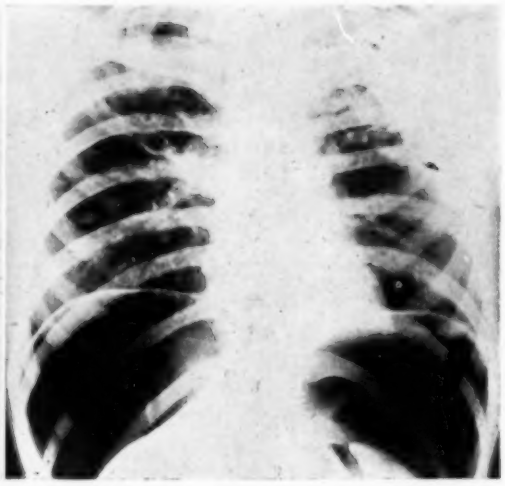

FIGURE 20

Fig. 18: Same case (L.N.) taken February 7, 1949, 38 days after P.A.S. treatment was completed. At this time more clearing was present, the cavities were lost to view, and the left lung was reexpanding.— *Fig. 19:* Same case on April 5, 1949, 57 days later after the introduction of pneumoperitoneum. Slightly more reexpansion on the left, but little other change.—*Fig. 20:* Same case on June 3, 1949, and showing slightly more clearing with a marked shrinking of the thin-walled annular shadow on the right. The lower annular shadow on the right has been lost to view.

Case 6: H.W., No. 61721, was a twenty-three-year-old white female waitress, divorced, with no children. The contact was unknown.

The Onset of the disease was with an upper respiratory infection in June, 1948.

The Past History is not significant. The patient suffered a G.U. or ovarian (?) disorder in 1948.

Present Illness: In June, 1948, the patient developed an upper respiratory infection accompanied by productive cough. This cleared in about ten days, but returned in September, accompanied by left chest pain and exertional dyspnea. The cough became increasingly severe, and night sweats began in November.

Physical Findings: The patient was 64 inches tall, weighing 121 pounds. Her pulse was 76.4 and regular, blood pressure was 110/40. She had a cough with expectoration of 1 cc. yellowish-white sputum, which was positive on culture. She complained of pain in the left lower chest on respiration. The x-ray film disclosed scattered exudative disease throughout the entire right upper lobe and in the upper two-thirds of the left lung. At least three large cavities (measuring 3 cm. in diameter) and numerous smaller ones were seen. Diagnosis, pulmonary tuberculosis, FAB. An x-ray film of the colon was suggestive of a disease process at ileacecal junction.

P.A.S. Treatment was begun on February 7, 1949. The blood count preceding treatment was as follows: Red blood corpuscles, 4,420,000; white blood cells, 9,300; hemoglobin, 74 per cent; sedimentation rate (Cutler method), 18 mm. in one-half hour.

Progress Notes: The patient gained eight pounds, her cough and expectoration decreased, and she felt better and stronger. Her temperature has remained normal. The x-ray inspection showed marked improvement with resolution of the exudative components and closure of the many cavities. On the latest film (May 13, 1949) no definite cavities were

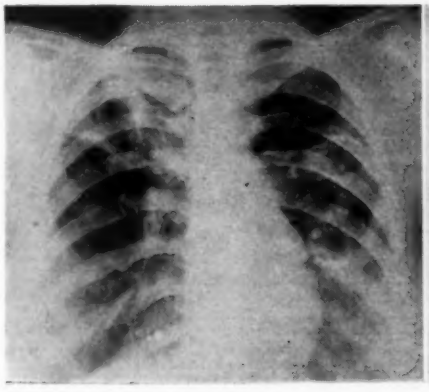

FIGURE 21

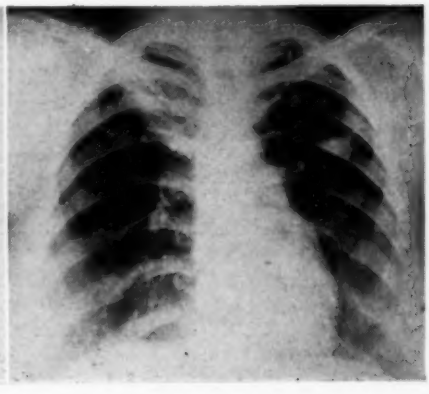

FIGURE 22

Fig. 21: Roentgenogram of Case 6 (H.W.) taken on January 19, 1947, 19 days before combined treatment of streptomycin and P.A.S. was begun. The streptomycin was given 45 days, and the P.A.S. was continued.—*Fig. 22:* Same case 95 days after treatment was begun, showing much clearing with a disappearance from view of large cavity in left upper lung field. The clinical condition was greatly improved, and the sputum was negative on concentration and culture since March 10, 1949.

visible. Improvement is still taking place. The sputum has been negative on concentration and on culture since March 10, 1949. On June 1, 1949, the red blood cell count was 4,610,000; white blood cells, 4,900; hemoglobin, 82 per cent; sedimentation rate, 3 mm. in one-half hour.

Although the cases are too few for statistical purposes, the results do indicate that there is a definite advantage—certainly no disadvantage—in a combined regimen.

The question of a delayed bacillary resistance to streptomycin was not established because the material was insufficient. Of the two cases formerly treated with streptomycin, one was resistant to 10 mcgms.; the other to 100 mcgms. The latter case turned sputum negative after three months of combined treatment.

Of the remaining seven cases, three turned negative before sixty days with none having a resistance to any more than 1 mcgm. streptomycin. Three others became slightly resistant to 10 mcgms. within five weeks' time, but thus far there has been practically no increase over that figure. The last case revealed partial resistance to 1.5 mcgms. two months after treatment, but turned negative and remained negative for six months. After nine months the sputum turned positive again, and the bacilli had a resistance to 10 mcgms.*

Forty of the cases treated one way or another with P.A.S. are assembled in Table I. There is some improvement in twenty-eight (70 per cent) of the forty cases deemed worthy of reporting at this time.

*We are grateful to Dr. Guy P. Youmans for the reports on sensitivity of the tubercle bacilli to streptomycin and P.A.S.

TABLE I

A Summary of 40 Cases Treated with P.A.S.

	Worse	Stationary	Sl. Imp.	Mod. Imp.	Marked Imp.	Total
Acute 'Exudative"	1	1	1	2	1	6
Ch. Fibro-Cas. and Ulc., 120 days	1	1	1	1	1	5
Ditto, 90 days		3	3	2		8
Ditto, 60 days		2	2	1		5
Streptomycin Failures	2	1	2		4	9
Comb. Streptomycin and P.A.S.			2	3	2	7
TOTAL	4	8	11	9	8	40

A Comparison of the Roentgenograms of all P.A.S. Treated Cases, Placebo Treated Controls, and a Group of Streptomycin Treated Cases

Adopting the method used by the Government Services to evaluate streptomycin treatment, we assembled all the roentgenograms of thirty-six completely treated P.A.S. cases, with twenty regularly treated streptomycin cases treated simultaneously and twenty fibro-ulcerative control cases who had been treated with a placebo or only with routine rest. Two of our colleagues (Berard and Brown) appraised each case according to the plan described earlier. Table II shows the result of this analysis. There was only a slight improvement in some of the placebo treated cases, such as would be expected under regular sanitarium treatment. The P.A.S. and streptomycin treated cases, on the other hand, revealed a gain that can only be interpreted on the basis of an intervention of something besides routine treatment. The results in the two (P.A.S. and streptomycin treated cases) were similar with little to choose between them. There was improvement in 75 per cent of the streptomycin treated cases and 70 per cent of the P.A.S. treated cases.

TABLE II

A Comparison of the Results of P.A.S. and Streptomycin Treated Cases with Controls

X-Ray Results 120 Days Rx.	Placebo Rx. (Chr. Fibroids) 20 pts.	P.A.S. (Chr. Fibroids) 16 pts.	P.A.S. 20 pts.	Streptomycin 20 pts.
Worse	15%	15%	10%	15%
Stationary	55%	33%	20%	10%
Slight Imp.	20%	33%	25%	15%
Moderate Imp.	5%	15%	10%	25%
Marked Imp.	5%	0%	35%	35%

The chronic fibroid group treated with P.A.S. did not fare so well, but still 48 per cent of this usually hopeless group of 16 cases showed temporary improvement. It should be borne in mind that the possibilities of rapid change in these cases rest only upon the clearing of peripheral infiltrates, some of which are not extensive and, therefore, do not register on the x-ray. The other changes consist of a slow removal of caseous foci, which change will probably not be fully revealed in the few months of observation.

The last change is that in the shape and size of the cavities and their walls. These changes are sometimes striking and consist of a shrinking of the cavities, a buckling and a thinning of the walls, sometimes to fine lines, or even to complete invisibility.

General Results

Toxic Effects of P.A.S.: One of the first problems to solve in any chemotherapeutic study is to note the possible drug toxicity in the therapeutic range, and the extent and nature of such toxicity.

P.A.S. appears, up to the present, to be relatively free from permanent toxic action. Nearly all patients experience a mild to severe sensation of nausea only during the first few days of treatment. Practically all the toxicity results from the drug's irritating action on the gastro-intestinal mucosa, resulting in nausea. Most patients were helped by the addition of aluminum hydroxide preparations. On rare occasions vomiting and diarrhea resulted, which could be controlled by removal of the drug or by administering belladonna or opium mixtures. Sometimes the toxic action was lessened and stopped by temporary reduction of the dosage. After a few days or weeks in such cases there appeared to be a development of tolerance so that the patient could continue the treatment through the required course. The drug should be given with the stomach filled if possible. Lehmann has recommended the use of "enteric" coated granules to prevent the action of the acid on the gastric mucosa. In addition, he contends that it facilitates a more uniform absorption. In our work we found very early that the toxic effect was reduced by giving the drug as an alkaline salt, although Lehmann contends that in the salt form, the drug is too quickly absorbed and eliminated. In only one case has treatment been discontinued entirely on account of gastro-intestinal symptoms.

In only one case was there an aggravation of an albuminuria already present, requiring discontinuation of treatment. A few patients developed skin reactions to varying degrees, but only one had to be taken off the drug on that account. No blood dyscrasias were found.

Whether any late effects will appear remains to be seen, but at the present time there do not seem to be any toxic effects that leave permanent damage, and very rarely is it necessary to discontinue treatment because of the temporary reactions.

Effect on Cough and Expectoration: Diminished cough was noted by 50 per cent of the patients on P.A.S. In the control group on placebo medication, improvement in cough occurred in 15 per cent.

Diminished expectoration was noted by most of the patients in whom cough improved.

Weight: In the group on placebo therapy, less than half showed a slight gain in weight. Of the patients on P.A.S., 70 per cent showed gains in weight, a few as much as twenty pounds or more during the period of observation.

Effect on Fever: Since many of the patients treated with P.A.S. were afebrile, the effect of P.A.S. on fever was studied in a group of twenty-four patients, who were seriously ill and failing. Alternate patients were given P.A.S., the others, the placebo preparation. At the end of three weeks, medication was stopped, and the effect evaluated one week later. Six of the twelve patients receiving P.A.S. showed a significant drop in fever. In two of them the fever rose promptly upon discontinuance of the drug. In the placebo group only two patients showed a decline in fever.

X-Ray Changes: We have considered the x-ray findings to be of the greatest interest and value in determining the effectiveness of this drug. The most marked improvements among the P.A.S. treated patients occurred in those with exudative lesions and those with tension cavities. Considerable clearing and great diminution in the size of such cavities was commonly noted. Among the chronic fibro-ulcerative cases improvement, if any, consisted of slight clearing of part of the lesions and slight diminution in the size of the cavities. No *great* difference could be seen between the group treated with P.A.S. and streptomycin and the group treated with streptomycin alone. In general, the cases manifesting a favorable response to P.A.S. showed the most marked improvement at the end of the four month period of treatment.

Changes in Laboratory Findings:

Conversion of Sputum: Sputum studies have been made, but have not been followed long enough after the end of treatment to give any significant results. There have been a few conversions of far advanced cases.

Blood Levels: Routine blood levels were always taken on the tenth day at 1:00 p. m. after treatment was begun. A 24-hour blood level curve was studied in a number of other patients. The curves were found to vary considerably in patients. At one and two hours after each dose, the blood levels were between 1.0 mg. per cent and 17.0 mg. per cent, averaging 2.83 mg. per cent. The level seems to rise during the afternoon and to fall off in the evening. There were only 1-3 mgs. of the drug in the blood stream at 2:00 a. m., six hours after the last daily dose, and practically

none by morning. The complete data will be given in a subsequent report.

Hemoglobin: With one exception (Case 2) no significant effect was noted on hemoglobin after four months of P.A.S. therapy or combined therapy in the patients studied. Patients who showed definite improvement in sedimentation rate often showed no change in hemoglobin. The large majority of patients, however, had no severe anemia before therapy.

Sedimentation Rates: Of patients on placebo therapy followed for four months, 15 per cent improved (Cutler method; 5 mm. or more improvement in 30 min. reading); 85 per cent were unimproved. Of patients treated with P.A.S. alone, 40 per cent showed improvement, with 60 per cent showing no improvement.. On combined therapy, 85.7 per cent showed improvement in the sedimentation rate. The sedimentation rate was not influenced by the blood level of P.A.S.

Resistance to P.A.S.: There were only three cases whose bacilli developed resistance to P.A.S.—one to 5, another to 25 mgs., and another to 100 mgs. Two were on long time treatment, and both have shown initial improvement with a later stationary or failing status. The x-ray film on D.W. (Figs. 3-8), show the deterioration of the pulmonary lesions corresponding approximately to the development of resistance. Another patient had a similar improvement followed by a deterioration and finally death. The third case was a placebo control at first, but was transferred to P.A.S. therapy. After less than a month a resistance to 100 mgs. per cent of P.A.S. developed. If these three cases are any indication, it would seem that about 10 per cent of the bacilli of cases on P.A.S. treatment will develop a significant resistance to the drug.

Discussion

The results of these rather limited experiments permit us to make some deductions regarding the effect of P.A.S. on pulmonary tuberculosis. Up to the present, we are able to state that P.A.S. exerts a decided favorable effect on some acute infiltrative lesions. The x-ray findings, the clinical effects, and laboratory changes noted were fairly comparable to the results observed in streptomycin treated cases, but were not always as clear-cut and did not appear as soon as observed in streptomycin treated cases.

In addition to the clearing of "exudative" disease, the drug appears to be of value to patients who have tension cavities. Many cavities shrink, and some become lost to view after P.A.S. treatment.

In chronic fibro-ulcerative tuberculosis, there is the same erratic effect on some cavernous types with and without infiltration as

are observed in similar cases treated with streptomycin. The one big difference is that germ resistance is not of great significance for P.A.S. A more prolonged study is mandatory in this type of case since the drug appears to be practically harmless, produces clinical improvement, and lessens cough and expectoration in many patients of this type.

A second course of P.A.S. therapy is being started in some of the patients who have finished a first course with apparent benefit, but whose disease was beginning to relapse. P.A.S. may be used simultaneously or alternately with streptomycin, either one following the other as the circumstances warrant. Likewise, surgery may be used at the appropriate time. Case 5 (L.N.) is a good example where pneumoperitoneum was used successfully. Case 2 was given a pneumothorax after treatment.

In the matter of delaying resistance to streptomycin in combined treatment, there is some indication that resistance to streptomycin is slightly delayed, but our series is too small to be significant.

Finally, the favorable results on about half the cases failing to respond to streptomycin treatment or recurring after a temporary improvement, without any other factor, will probably insure P.A.S. a permanent role in the treatment of pulmonary tuberculosis. The drug lends itself to prolonged courses of treatment, which may produce even better results than have already been reported.

CONCLUSION

P.A.S. therapy was of considerable benefit when used on patients having pulmonary tuberculosis with exudative disease and tension cavities. It appears to have a definite effect on a few cases of chronic fibro-ulcerative tuberculosis, although the majority were not benefited. When used after streptomycin has failed, it improved nearly 50 per cent of the cases treated.

The drug does not appear to produce any marked resistance in tubercle bacilli. It does not seem to possess any permanent toxic effect when properly administered. For these various reasons, therefore, P.A.S. appears to have a definite field of usefulness in the treatment of pulmonary tuberculosis.

CONCLUSION

La terapia con el P.A.S. hizo mucho provecho cuando se le empleó en tuberculosos pulmonares con lesiones exudativas y cavidades de tensión. Parece tener un efecto bien definido en unos pocos casos de tuberculosis fibro-ulcerativa crónica, aunque en la mayoria no hizo provecho. Cuando se le empleó en casos en

los que había fallado la estreptomicina, mejoraron casi el 50 por ciento de los casos tratados.

La droga no parece producir decidida resistencia en los bacilos de Koch. Tampoco parece tener ningun efecto tóxico permanente cuando se la administra apropiadamente. Por estas varias razones se considera que el P.A.S. parece tener un lugar bien definido en el tratamiento de la tuberculosis pulmonar.

REFERENCES

1 Lehmann, Jorgen: "Chemotherapy of Tuberculosis. The Bacteriostatic Action of P-aminosalicylic Acid (PAS) and Closely Related Compounds Upon the Tubercle Bacillus, Together with Animal Experiments and Clinical Trials with PAS," (In Swedish), *Svenska Lakartidningen,* 43: 2029, 1946.

2 Lehmann, Jorgen: "Para-aminosalicylic Acid in Treatment of Tuberculosis: Preliminary Communication," *Lancet,* 250:15, 1946.

3 Bernheim, F.: "The Effect of Various Substances on the Uptake of Tubercle Bacillus," *J. of Bacteriology,* 41:387, 1941.

4 Sievers, Olof: "Experimental Trials with P-aminosalicylic Acid (PAS) Against Various Kinds of Bacteria," (In Swedish), *Svenska Lakartidningen,* 43:2041, 1946.

5 Vallentin, Gylfe, et al: "On the Treatment of Pulmonary Tuberculosis with Para-aminosalicylic Acid (PAS)," Paper presented at the Scandinavian Tuberculosis Congress, Copenhagen, June 25-27, 1948.

6 Alin, K. and Difs, H.: "Clinical Experiences with P-aminosalicylic Acid (PAS) in Pulmonary Tuberculosis. 1. Therapeutic Experiments with PAS. Absorption and Excretion of PAS," (In Swedish), *Nordisk Med.,* 33:151, 1947.

7 Dempsey, T. G. and Logg, M. H.: "Para-aminosalicylic Acid in Tuberculosis. Early Results of Clinical Trials," *Lancet,* 253:871, 1947.

8 Lemming, Rolf: "Skin Tuberculosis Treated with Para-aminosalicylic Acid," *Lancet,* 256:200, 1949.

9 Carstensen, Bo and Sjolin, Stig: "Para-aminosalicylsra (PAS) vid lungtuberkulos med sekundat tarmtuberkulos," *Svenska Lakartidningen,* nr. 16, 1948.

10 Youmans, G. P.: "The Effect of Para-aminosalicylic Acid in Vitro and in Vivo on Virulent Human Type Tubercle Bacilli," *Quart. Bull, North-Western Univ. Med. School,* 20:420, 1946.

11 Feldman, W. H., Karlson, A. G. and Hinshaw, H. C.: "Para-aminosalicylic Acid in Experimental Tuberculosis in Guinea Pigs," *Proc. Staff Meet.,* Mayo Clinic, 22:473, 1947.

12 Youmans, G. P., Youmans, A. S. and Osborne, R. R.: "Combined Effect of Streptomycin and P-aminosalicylic Acid on Experimental Tuberculosis in Mice," *Journal Lancet,* 67:403, 1947.

13 Karlson, Alfred G., Pfeutze, Karl H., Carr, David T., Feldman, William H. and Hinshaw, H. Corwin: "The Effect of Combined Therapy with Streptomycin, Para-aminosalicylic Acid and Promin on the Emergence of Streptomycin-Resistant Strains of Tubercle Bacilli: A Preliminary Report," *Proc. Staff. Meet.,* Mayo Clinic, 24:85, 1949.

14 Vennesland, K., Ebert, R. H. and Bloch, R. G.: "In Vitro Effect of Streptomycin and Para-aminosalicylic Acid (PAS) on the Growth of Tubercle Bacilli," *Proc. Society for Exper Biol. and Med.,* 68:250, 1948.

Discussion

JOHN S. PACKARD, M.D., F.C.C.P.
Allenwood, Pennsylvania

We have treated 27 patients at Devitt's Camp with P.A.S. for a period of from one to four months, and all patients are still under treatment. They fall into the following groups: Acute exudative, 1; Chronic fibroid, 5; Previously treated with streptomycin, 15; Silico-tuberculosis, 3; Far advanced extremely ill, 1; Combined P.A.S. and streptomycin, 1; Tuberculous enteritis complicating pulmonary tuberculosis, 1.

Dosage was maintained at 15 grams daily in six divided oral doses at three hour intervals from 7 a. m. to 10 p. m. Symptoms attributed to the drug were nausea, gas, diarrhea of varying degree, and these were controlled by Kaopectate or Kaomagma.

It is too early to evaluate treatment, but our results so far seem to parallel those of Dr. Sweanys' in his excellent preliminary report. Our best results were in the exudative lesions and in those patients who had ceased to improve under streptomycin or who had relapse following streptomycin.

X-ray improvement follows clinical improvement, but usually proceeds more slowly than with streptomycin. The improvement continues, however, at a steady and encouraging pace. Cavities show an encouraging decrease in size and some, including those of the tension type, have apparently closed. The case of tuberculous enteritis showed a remission of symptoms, after a recurrence during previous streptomycin.

I shall present three cases to illustrate reduction in cavities.

Case 1: I.K., white, female, age 63. No improvement on bed rest only for seven months, with exudative disease left lung, severe cough, recurrent hemoptyses. P.A.S. for three months with marked clinical improvement, and clearing on x-ray with disappearance of small cavities.

Case 2: D.S., white, female, age 41. Long history of bilateral disease. Recent acute flare-up left lung with consolidation and ballooning of cavity following termination of streptomycin treatment. Marked clinical improvement after one month under P.A.S. and definite x-ray clearing and reduction in size of cavity.

Case 3: H.K., white, female, age 32. Appearance of tension type cavity in left lower lobe after clearing of exudative disease under streptomycin. The cavity was no longer visible after two weeks of P.A.S. and treatment with the drug was continued, combined with pneumoperitoneum and left phrenic crush. Sputum negative on direct smear.

It seems logical to use P.A.S. as a continuation treatment after streptomycin and to combine it with collapse therapy. One can

thus avoid or postpone development of resistant strains and can enhance the value of collapse therapy. One can also expect to use P.A.S. as a preliminary to thoracoplasty and resection, as was done in one of our cases.

GEORGE SIMMONS, M.D.
New York, New York

Drs. Lamberta, Klopstock and myself have studied the effect of combined streptomycin and P.A.S. therapy in approximately 40 patients in the course of the last year at Triboro Hospital. The basis for such treatment was the conception that this combination of drugs may be able to upset the nutritional-chemical environment in such a way that tubercle bacilli may not become adapted to streptomycin, that is that the emergence of streptomycin resistant organisms may be prevented.

Reports from other sources as well as results obtained at Triboro Hospital seem to confirm the impression that streptomycin-fastness is delayed or prevented if P.A.S. is added to a streptomycin regime. I would like to present some figures, substantiating this impression. In representative cases a total of 62, 84 and 210 grams of streptomycin was given over a period of 133, 84 and 210 days respectively together with a standard dose of six grams of P.A.S. daily. The occurrence of streptomycin resistant strains was either delayed or prevented. In contrast to this 50 per cent of a group of 70 patients given streptomycin alone showed resistant organisms at the end of a six week course and only 25 per cent of germs isolated were sensitive to less than 25 micrograms of streptomycin.

Even though statistical data are not available yet, it appears that delay or prevention of streptomycin-fastness is a frequent, if not a constant feature of combined P.A.S. and streptomycin therapy. In our experience this combined therapy has occasionally given dramatic results.

CASE REPORTS

Case 1: A young colored girl developed a massive hematogeous post-pneumonectomy spread while under streptomycin. She was running a spiking temperature up to 105 degrees F., she went on spreading rapidly even though she was receiving one gram of streptomycin daily, she was in an oxygen tent and the prognosis was entirely hopeless. One week after addition of PAS to the streptomycin regime the temperature subsided, today she is afebrile, not dyspnoic and is able to be up and about. The degree of involvement and the rate of progression of the disease were such that spontaneous remission is difficult to conceive and it appears that in this case PAS was actually lifesaving.

Case 2: A patient with a completely destroyed right lung and progressive cavitary disease on the contralateral side did not show any significant response to conventional streptomycin therapy. A prolonged course of PAS and streptomycin brought about arrest of progression on the left and eliminated all clinical symptoms. The sputum has remained negative on numerous examinations, whereas before it had been persistently positive. As a rule, however, x-ray changes observed are slight and are not at all proportionate to the improvement of the patient's general condition.

Case 3: This patient's pulmonary tuberculosis was of many years' standing. A left pneumothorax had resulted in an inexpansable lung and following pregnancy a massive flare-up occurred on the contralateral side. Eventually a left decortication and a right thoracoplasty were performed and she had several courses of streptomycin which had left her streptomycin resistant.

A few months after the decortication two large cavities developed in this lung, the sputum turned frankly positive on smear and she started suffering frequent febrile episodes, probably due to sputum retention. A double cavernostomy was performed and daily application of PAS to both cavities was started. Two weeks following the cavernostomy the scanty secretions were negative for tubercle bacilli on both concentrates and cultures and so were all gastric lavages. After one month of such local treatment PAS became inavailable for awhile and a distinct increase in the amount of daily secretions was noticed. Reinstitution of local PAS treatment resulted in disappearance of secretions. For the last three months no PAS has been used and the small residual cavities have remained sterile.

Acknowledgement: The PAS used in this study was generously donated by Merck and Company and by Panray Company.

JORGEN LEHMANN, M.D., F.C.C.P.
Gothenburg, Sweden

Thank you for your kind invitation to attend this meeting and to take part in the discussion. First I want to congratulate Dr. Sweany on his fine presentation of the treatment of pulmonary tuberculosis with PAS. The results are similar to those we have achieved in Sweden—in fact, some of Dr. Sweany's patients showed a more dramatic improvement than I have seen.

In Sweden we have made a follow up of 378 cases of pulmonary tuberculosis treated with PAS in six sanatoria. If I should compare the results with those achieved in this country with streptomycin, I would say, that we have seen a faster decrease in temperature and sedimentation rate during PAS treatment, whereas the resolution of the pulmonary lesions seems to go faster during streptomycin treatment. The frequency of conversion of sputum is about the same with the two drugs, the later observa-

tions however are much better with PAS—presumably due to the low frequency of emergence of resistance to PAS.

Recently it has been shown in this country, that PAS in combination with streptomycin depresses the frequency of emergence of resistance to streptomycin—both in vitro and in clinical trials. Therefore, a combined therapy seems advisable. However, to be able to evaluate the effect of such a combination we must know the effect of each of the drugs *per se*. I am therefore glad to see that Dr. Sweany has started the treatment with PAS alone in this country, where you have an extense experience with streptomycin therapy and therefore can better evaluate the different forms of therapy.

The Effect of Streptomycin with Para-Amino Salicylic Acid on the Emergence of Resistant Strains of Tubercle Bacilli[1,2,3]

EDWARD DUNNER, M.D., F.C.C.P.,[4] WALTER B. BROWN, M.D.[5] and JACK WALLACE[6]

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In order to determine the effects of combined streptomycin and para-aminosalicylic acid therapy on the emergence of resistant strains of tubercle bacilli, 11 patients received both drugs for 120 days from July, 1948 to January, 1949. None had received previous streptomycin or para-aminosalicylic acid therapy. Cultures for tubercle bacilli were taken every two weeks and determinations of sensitivity made on all those which were positive.

Clinical Material: All patients were white males with far advanced active pulmonary tuberculosis. Nine were between 51 and 58 years of age; one was 49 and the youngest was 38. Streptomycin, 1.0 gm. intramuscularly and para-aminosalicylic acid, 15.0 gm., administered orally in three equal doses per day were prescribed for 120 days.

Response to Treatment (Roentgenographic): Patients were selected whose roentgenograms showed components suggesting that they would probably contribute positive cultures for the duration of the treatment period. A comparison of roentgenograms at the beginning and end of treatment showed moderate improvement in four; slight improvement in five and no appreciable change in two. It cannot be definitely stated that the changes observed could not have been obtained by streptomycin therapy alone.

Clinical Observations: The beneficial effects of streptomycin on cough, sputum, temperature and weight are well known.[7] However, the "tonic effect" which is usually apparent soon after beginning treatment with streptomycin was not evident as a result of the

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[1]Read before the Seventh Veterans Administration Streptomycin Conference, Denver, Colorado, April, 1949.

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diffuse gastro-intestinal discomfort produced by para-aminosalicylic acid.

Weight: The weight gains at the end of treatment were disappointing except in two patients who gained 29 and 6 pounds respectively. The weight in five patients remained unchanged; four lost approximately 6 pounds each. This was in marked contrast to the 20 pound average weight gain in patients with exudative disease previously treated at this institution with streptomycin alone.[8] An explanation of the difference lies in the fact that during the early months of treatment most patients had a diarrhea attributable to para-aminosalicylic acid with resultant weight losses up to 15 pounds. This was, in most patients, regained during the second half of the treatment period when gastro-intestinal symptoms became less prominent.

Temperature: In nine patients, temperature remained normal throughout treatment. In one patient with 100.4 degrees fever at the start of therapy, defervescence took place within the first week and remained normal. The eleventh patient had a temperature elevation to 100 degrees from the third to the fourth month of treatment. A rise in temperature did not occur in any of the patients when the drugs were discontinued.

Laboratory Data

Sedimentation rates: All of the patients had elevated sedimentation rates before therapy was instituted. These ranged from 21 mm. to 30 mm. per hour (Cutler Method). The rate dropped to 11 mm. per hour in two patients and remained substantially unchanged in nine.

Sputum Conversion: At the end of therapy concentrated sputa specimens were negative for tubercle bacilli in four of the eleven patients. By performing repeated sputa examinations it was possible to obtain at least one positive sputum from each patient so that final sensitivity studies could be performed. However, the four patients have subsequently remained negative on concentration and gastric lavage cultures. Tracheal washings were not performed.

Sensitivity Tests: Tubercle bacilli obtained from each patient just prior to the institution of treatment were inhibited *in vitro* by less than 1.0 mcg. streptomycin per milliliter of medium. Sensitivity studies after 60 days of combined therapy showed that the bacilli were still sensitive in all 11 patients. The data from the Seventh Streptomycin Conference, Denver, Colorado, April, 1949,[9] relative to resistance studies in patients treated with combined therapy, comprised 34 patients. After 45 days of treatment, resistance studies in 22 patients showed only one developing resis-

tant bacilli; after 60 days of treatment, resistance studies in 26 patients only showed three or 12 per cent developing resistant bacilli. On the other hand, the data compiled from a large series of patients using streptomycin alone showed 50 per cent with resistant strains after 60 days treatment. The results were consistent and regardless of whether the patients were treated with 1.8, 1.0 or 0.5 gm. streptomycin daily. This apparent delay in the emergence of resistance is further suggested by comparison data for the second, third and fourth months of treatment as given in the table below.

Development of Resistance by Tubercle Bacilli to Streptomycin

STREPTOMYCIN REGIMENS	MONTHS OF TREATMENT		
	2nd	3rd	4th
1.8 - 2.0 gm SM/120 days	50%	66%	74%
1.0 gm SM/120 days	49%	59%	63%
0.5 gm SM/120 days	47%	63%	77%
1.0 gm SM & PAS/120 days	12%	16%	42%

The clinical importance of using antimicrobial agents to prevent or delay the occurrence of resistant micro-organisms is obvious. Comparison of the results of this investigation with reports on the emergence of streptomycin resistant strains of tubercle bacilli when streptomycin alone was administered in the treatment of tuberculosis suggests that combined therapy delays the emergence of such resistant strains. This delay in the emergence of resistant strains by using combined therapy has also been suggested in a preliminary report from the Division of Experimental Medicine, Mayo Foundation with the use of streptomycin, para-aminosalicylic acid and promin.[10]

Toxemic Manifestations

Renal Irritation: No patient displayed any diminution in kidney function. Five patients excreted urinary casts at some time during the therapy period, but their appearance was transitory. In three a trace of albuminuria was observed but despite continuation of therapy, it disappeared.

Allergic Manifestations: Intermittent eosinophilia of from 6 to 14 per cent was noted in seven patients. Dermatitis appeared in two patients.

Para-aminosalicylic Acid Toxicity: With a daily dosage of 15 gm. para-aminosalicylic acid, an average blood level of 3 to 7 mgm. per cent was obtained four hours after the oral dose (Ehrlich

Method). Unfortunately, a study of our data does not permit a definite conclusion as to whether para-aminosalicylic blood levels should be maintained for therapeutic efficacy as in the case of sulfones, or whether they need not be constant, as with streptomycin therapy.

Diffuse gastro-intestinal discomfort and diarrhea were disturbing factors during the early weeks of treatment. The addition of equal parts of sodium bicarbonate was helpful in reducing the gastric irritation. The Swedish workers have employed a "granule" preparation of the drug with an enteric coating.

Because of the close structural similarity of para-aminosalicylic and salicylic acid, several prothrombin times were determined on four of the treated patients. These were normal.

Para-Aminosalicylic Acid (PAS)

Lehmann,[11] Vallentin,[12] and Alin and Difs[13] have described preliminary observations on the use of para-aminosalicylic acid in human tuberculosis. According to their reports, PAS appears to have a definite chemotherapeutic effect in human tuberculosis.

Youmans[14] has examined the combined effects of streptomycin and para-aminosalicylic acid in experimental tuberculosis in mice. Combination of the two drugs resulted in a better therapeutic response than when either was given separately.

The synergistic action of the drugs in combination, plus the suggested delay in the emergence of streptomycin resistance, is of great clinical importance.

Two additional questions appear of some interest: (1) Are streptomycin-resistant bacilli sensitive to para-aminosalicylic acid? (2) Do tubercle bacilli develop resistance to para-aminosalicylic acid?

PAS sensitivity studies were performed, *in vitro*, on streptomycin resistant tubercle bacilli from 34 patients. The results showed that in each case, growth was inhibited by concentrations of 0.2 mgm. per 100 cc. para-aminosalicylic acid or less. All cultures tested were obtained from sputa except in two patients from whom pleural fluid and material from a draining sinus were used. It is concluded that streptomycin-resistant tubercle bacilli are sensitive to para-aminosalicylic acid *in vitro*.

Para-aminosalicylic acid sensitivity tests were performed after 120 days therapy in the 11 treated cases; they showed that in six patients, tubercle bacilli were inhibited by 0.3 mgm. per cent or less; in two, they were inhibited by 5 mgm. per cent, and in three they were not inhibited by 20 mgm. per cent. This indicates that resistance to para-aminosalicylic acid may develop.

SUMMARY AND CONCLUSIONS

In a pilot study to observe the rate of development of resistant strains of tubercle bacilli by the use of streptomycin and para-aminosalicylic acid, it appears that development of such strains is delayed.

Streptomycin-resistant tubercle bacilli are sensitive to para-aminosalicylic acid *in vitro*.

Strains of tubercle bacilli in three patients appeared to develop resistance to para-aminosalicylic acid. This matter needs further investigation.

Fifteen grams of para-aminosalicylic acid per day caused gastro intestinal disturbance with nausea, emesis and diarrhea. Blood levels ranged from 3 to 7 mgm. per cent four hours after PAS administration. Whether certain specific blood level maintenance is required for therapeutic efficacy requires further study. Prothrombin time was not altered by the above dosage.

RESUMEN Y CONCLUSIONES

En un estudio preliminar para observar el grado de desarrollo de las cepas resitentes a la estreptomicina después del uso de ésta y del ácido para-amino-salicílico, parece que tal desarrollo es demorado.

Los bacilos estreptomicinorresistentes son sensibles al ácido para-amino-salicílico in vitro.

En tres enfermos se encontró que sus cepas de bacilo tuberculoso desarrollaron resistencia al ácido para-amino-salicilico. Esto necesita una investigación ulterior.

Las dosis de quince gramos de ácido para-amino-salicílico por dia provocaron trastornos gastro-intestinales con nausea, vómitos y diarrea.

Los niveles en la sangre variaron de 3 a 7 mg. por ciento. Para determinar si para obtener resultado terapéutico se requiere cierto tenor de la droga en la sangre, se necesita estudio mas prolongado.

El tiempo de protrombina no fué alterado por la dosificación señalada.

REFERENCES

7 "The Effect of Streptomycin Upon Pulmonary Tuberculosis; Preliminary Report of a Cooperative Study of 223 Patients by the Army, Navy and Veterans Administration," prepared by the Streptomycin Committee, Veterans Administration, Washington, D. C., *Am. Rev. Tuberc.*, 56:485, 1947.

8 Cassidy, W. A. and Dunner, E.: "Pulmonary Tuberculosis Treated with Streptomycin," *Am. Rev. Tuberc.*, 56:552, 1947.

9 Veterans Administration: "Minutes of Seventh Streptomycin Conference," April, 1949.

10 Karlson, A. G., Pfuetze, K. H., Carr, David T. and Feldman, W. H.: "The Effect of Combined Therapy with Streptomycin, Para-Aminosalicylic Acid and Promin on the Emergence of Streptomycin Resistant

Strains of Tubercle Bacilli: A Preliminary Report," *Proc. Staff Meet.*, Mayo Clinic, 24:85, 1949.
11 Lehmann, J.: "Para-Aminosalicylic Acid in the Treatment of Tuberculosis," *Lancet*, 1:15, 1946.
12 Vallentin, G.: "Clinical Experiences in the Treatment of Pulmonary Tuberculosis with PAS," *Svenska Lakartidningen.*, 43:2047, 1946.
13 Alin, K. and Difs, H.: "Clinical Experience with PAS," *Nordick Medicin*, 33:151,1947.
14 Youmans, G. P. and Williston, E. H.: "The Effect of Streptomycin on Experimental Infections Produced in Mice with Streptomycin-resistant Strains of M. Tuberculosis Ver. Hominis," *Proc. Soc. Exp. Biol. Med.*, 63:131, 1946.

The Occurrence of Tubercle Bacilli Resistant to P-aminosalicylic Acid (PAS)

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The demonstration by Youmans and associates[1] of streptomycin-resistant tubercle bacilli in eight of 12 patients in the first clinical trials of this drug was soon followed by reports from many other workers showing that streptomycin-resistant tubercle bacilli regularly occur in a certain percentage of patients receiving this antibiotic. The occurrence of streptomycin-resistant tubercle bacilli is now a well-known problem and is the subject of much publication. In contrast, however, is the situation with regard to para-aminosalicylic acid (PAS). In spite of the extensive use of PAS in experimental and clinical tuberculosis since 1946, when Lehmann[2] first described the tuberculostatic properties of this agent, there has been very little written on the subject of PAS-resistant tubercle bacilli.

Most of the few reports on the in vitro sensitivity of human tubercle bacilli to PAS indicate that human tubercle bacilli are sensitive to a low narrow range of concentration of PAS. Youmans,[3] using Proskauer and Beck liquid medium, found that 12 strains of human tubercle bacilli, of which six were streptomycin-resistant, were sensitive in vitro to concentrations of PAS between 0.019 and 0.156 mg. per 100 ml. of medium. Sievers,[4] who used a modified Pryce slide culture procedure, reported that the tubercle bacilli in sputum and from pure cultures were all sensitive to PAS in concentrations ranging from 0.0153 to 0.153 mg. per 100 ml. of medium. Youmans and associates[5] augmented their previous observations and found that 17 cultures of human-type tubercle bacilli, of which six were streptomycin resistant, and one bovine strain of tubercle bacilli were all sensitive in vitro to 0.156 mg. or less of PAS per 100 ml. of medium. Most of the strains were inhibited by less than 0.039 mg. of PAS per 100 ml. of medium. We[6] have used egg-yolk agar medium containing sodium para-

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aminosalicylic acid (NaPAS) in twofold dilutions ranging from 0.006 to 6.4 mg. of NaPAS per 100 ml. of medium and have reported that cultures from 71 patients who had not received PAS were sensitive to 0.012 to 0.025 mg. of NaPAS per 100 ml. of medium.

Hurni[7] found that two of four freshly isolated strains of human-type tubercle bacilli could be made to grow in 30,000 times the original concentration of streptomycin after four passages in Dubos' medium containing the antibiotic. The other two strains required nine passages before showing ability to grow in high concentrations of streptomycin. For PAS, however, it required eight passages before growth was seen in as much as ten times the original concentration of PAS. Hurni did not consider this to be true PAS resistance and stated that if resistance to PAS does develop at all it does so very slowly as compared to streptomycin resistance. Sievers[8] reported that tubercle bacilli will not continue to grow in concentrations of PAS greater than 0.015 mg. per 100 ml. of medium using the slide culture technic and that he had not observed any consistent resistance to PAS in numerous specimens from patients treated with this substance. Eastlake and Barach[9] found that cultures from untreated patients were resistant to only 0.078 mg. of PAS per 100 ml. of medium but that cultures from three other patients who had received 210, 630 and 1,000 gm. of PAS respectively were resistant respectively to 2.5 mg., 0.63 mg. and 0.63 mg. of PAS per 100 ml. They stated that either strains vary in their sensitivity to PAS or else some degree of resistance did develop.

Widstrom and Swedberg,[10,11] using Dubos' medium, reported finding a considerable difference in sensitivity to PAS among various strains of tubercle bacilli. They found that a number of human-type strains and the Ravenel bovine strain were resistant to at least 10 mg. of PAS per 100 ml. of medium. Swedberg and Widstrom[12,13] have also written that no beneficial effect of PAS therapy could be seen in mice infected with the PAS-resistant Ravenel strain. Widstrom and Swedberg[11,14] have found that PAS-resistant cultures of tubercle bacilli may be isolated from some patients after prolonged treatment with this substance and that mice infected with such strains will not respond to treatment with PAS. Sweany[15] stated that "we have found in from 5 to 10 per cent of our treated cases an unstable type of bacillary resistance to PAS which fluctuates considerably. About half of these cases developed a complete resistance to 10 mg. of PAS per 100 ml. of medium and showed a corresponding deterioration of the patient's clinical course. Some of the other patients who have shown slight or partial resistance to 10 mg. of PAS have made considerable clinical improvement. The final evaluation of this phenom-

enon is not yet possible." Odelberg[16] reported that in a series of 79 patients treated with PAS for at least 184 days five were found to have PAS-resistant tubercle bacilli. These patients were treated with PAS at the rate of 10 to 15 gm. daily with a short period of three to four days of no treatment every five weeks. They also received a short course of streptomycin therapy of 1 gm. a day for one to two weeks only. Dunner and associates[17] reported that PAS-resistant tubercle bacilli were found after treatment in three of 11 patients who received 15 gm. of PAS and 1 gm. of streptomycin daily for 120 days.

We[6] previously reported finding PAS-resistant tubercle bacilli in four of five patients treated with PAS alone for periods of 157 to 251 days. These cultures were able to grow in medium containing 200 to 500 times as much NaPAS as was required to inhibit the growth of cultures isolated from the same patients before treatment was started. Two of these patients had streptomycin-resistant tubercle bacilli prior to treatment with PAS and the cultures finally isolated were resistant in vitro to both antituberculosis agents. Of particular interest was the finding that there was no demonstrable increase of resistance to streptomycin or to PAS in the case of four patients who were treated approximately the same length of time with PAS, streptomycin and promin. An in vivo test in guinea pigs using a PAS-sensitive tubercle bacillus and a PAS-resistant strain from the same patient showed that no favorable therapeutic effect was caused by treatment with PAS in the infection due to the PAS-resistant strain, in contrast to the beneficial effect of the treatment in the animals infected with the PAS-sensitive strain.[18]

We have extended our studies on the in vitro sensitivity to PAS of tubercle bacilli isolated from patients who had not received PAS and from patients treated with PAS alone or in combination with streptomycin and promin. The data to be presented include our previously published observations.[6,19]

Methods

The in vitro tests were done with egg-yolk agar medium[20] containing four fold concentrations of PAS ranging from 0.0045 mg. to 4.608 mg. per 100 ml. of medium. Higher concentrations were used in some instances when cultures were found to be resistant to more than 4.608 mg. per 100 ml. We have found that the differences in the amount of growth are more easily detected on this solid medium than in liquid medium. Furthermore, it is possible to select single colonies from solid medium for further study. The medium is easily prepared by adding the yolk of one egg to 120 ml. of sterile melted and cooled nutrient agar. Because

of its greater solubility a calculated amount of NaPAS is used to give the desired amount of PAS. (Previously we expressed PAS sensitivity in terms of the concentration of NaPAS $2H_2O$ but to conform to the usage of others we now express the concentration in terms of the actual amount of PAS.) The desired solutions of NaPAS are sterilized by filtration and added to the melted nutrient agar immediately before the egg yolk is added. (It is more practical to sterilize by filtration the most concentrated solution to be used. Fourfold dilutions can be made from the single sterile solution by using sterile distilled water.) The nutrient agar, NaPAS and egg yolk are mixed by shaking and then poured into sterile test tubes which are placed in the slanted position to harden.

The inoculum is prepared by grinding in a mortar several loopfuls of the culture to be examined and adding enough sterile water to make a suspension approximately equivalent to 1 mg. per milliliter. The accuracy of making this suspension is not critical, for we have found that a tenfold variation in the concentration of tubercle bacilli will not significantly affect the results. Each tube of medium containing PAS plus a control tube is inoculated with 0.1 ml. of the suspension. After 14 days of incu-

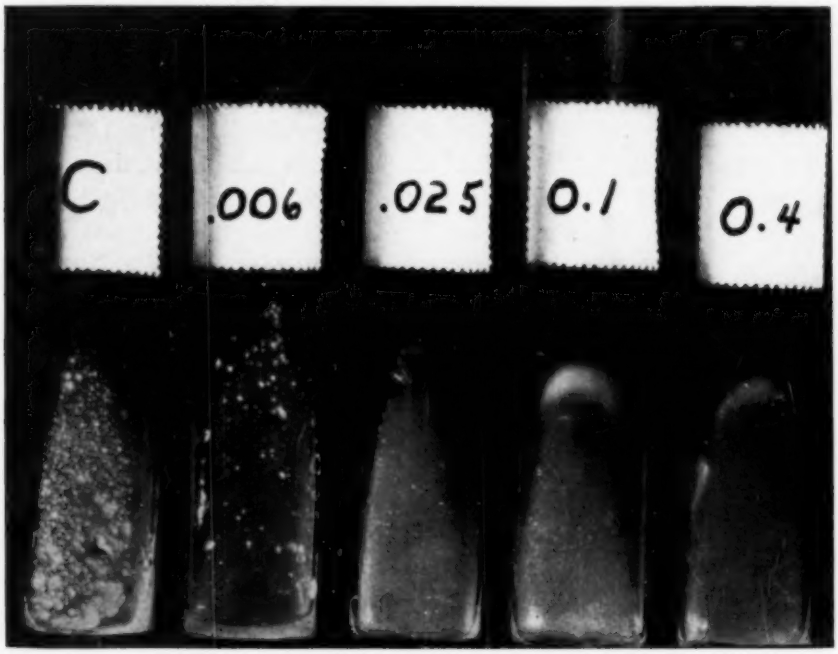

FIGURE 1: PAS sensitive culture after 28 days of growth. The concentration of PAS per 100 ml. of egg-yolk agar is indicated on each tube. After 14 days of incubation there was luxuriant growth on the control tube only and the resistance to PAS was recorded as ▲0.006. After an additional 14 days of incubation, growth appeared only on the tube containing 0.006 mg. of PAS per 100 ml. of medium.

▲Signifies "less than."

bation the resistance of the culture to PAS is recorded as the maximal concentration which permits growth.

We formerly recorded the results after 14 days and again after 28 days of incubation and found that there was no significant increase in the amount of growth. At most there was growth only in the tube containing the next highest concentration of PAS after an additional incubation of 14 days.

Results

Including those previously reported[6] we have examined 107 cultures of human-type tubercle bacilli and two cultures of bovine tubercle bacilli. All of these, including 15 human-type cultures which were resistant to streptomycin, were sensitive to a low narrow range of concentration of PAS. Ninety-five per cent of the human type cultures were resistant to only 0.018 mg. or less of PAS per 100 ml. of medium. Four were resistant to 0.072 mg. and 1 culture gave good growth in medium containing 0.144 mg. of PAS per 100 ml. of medium. The two bovine strains were resistant to not more than 0.018 mg. of PAS per 100 ml. of medium. The variations that did occur were represented by differences in growth on one or two tubes which, upon repeated tests, were

FIGURE 2: PAS-resistant culture from patient 7 in table 1. The growth on the tube containing 6.4 mg. of PAS per 100 ml. of medium was subsequently found to be resistant to more than 32.8 mg. of PAS per 100 ml. The difference in the amount of growth on the control tube and on the higher concentrations of PAS suggests that there may be a mixture of PAS-sensitive and PAS-resistant bacilli.

found to be within the limits of accuracy of the procedure. Figure 1 shows the results of a test on a culture from a patient who had not received PAS.

Our experience with patients treated with PAS alone for prolonged periods is limited to 8 cases. From four of these it was possible to isolate tubercle bacilli which were resistant in vitro to high concentrations of PAS, as shown in Table 1. This group is too small to allow for any conclusions regarding the incidence of the occurrence of PAS-resistant tubercle bacilli. Clinical studies are too limited to date to determine the correlation between the sensitivity of the strains in each case and the response to therapy. It is unfortunate that a culture was not obtained for sensitivity tests prior to therapy from patient two, but it may be assumed that the culture was probably not unlike other cultures from patients who have not received PAS. Figure 2 shows a PAS-sensitivity test on a culture from patient seven in Table 1. The growth on the tubes containing PAS is less than that on the control, suggesting that there is a mixture of PAS-sensitive and

TABLE 1

In Vitro Resistance to PAS of Tubercle Bacilli Isolated From Patients After Extensive Treatment With PAS

Patient's number	Duration of treatment days	Approximate daily dose, gm.	Total dose, gm.	Resistance to PAS* Before treatment	Resistance to PAS* After treatment
1†	90	**	2,096	Not done	0.004
2†	267	8 to 10	2,250	Not done	♦4.608
3†	131	2 to 10	391	0.072	1.150
4	165	9.6	1,760	0.004	0.004
5†	183	8 to 10	1,650	0.004	♦2.300
6	96	10 to 15	1,020	Not done	0.004
7§	185	10	1,850	0.004	♦6.4††
8§	248	10	2,480	Not done	0.004

*Maximal concentration of PAS in milligrams per 100 ml. of medium which permitted growth.

†Cultures from these patients were resistant to streptomycin before PAS therapy was started.

**Up to 30 gm. of NaPAS intravenously per day with 14.4 gm. of PAS orally during the last 30 days.

§These patients received 1 gm. of streptomycin daily plus 10 gm. of PAS daily for one month, followed by treatment with PAS alone for five months.

††This culture was used to infect mice and when reisolated from the animals it was found to grow in ♦32.8 mg. of PAS per 100 ml. of medium.

♦Signifies "greater than."

PAS-resistant tubercle bacilli. The final cultures from patients two and five were tested on medium containing streptomycin and PAS and were found to be resistant in vitro to both agents.

Table 2 presents observations made on a series of patients treated with PAS, promin and streptomycin. Each patient received 0.5 gm. of streptomycin once daily, 5 to 10 gm. of PAS daily in four divided doses and 5 gm. of promin intravenously per day for the first 14 days of each 21-day period, except for patients 15 and 16 who received no promin.

Only patient 10 was found to have streptomycin resistant tubercle bacilli after the combined treatment. Even though the series is small, this is much lower than the number of patients who would be expected to discharge streptomycin-resistant tubercle bacilli after treatment with streptomycin alone.[18] Of particular interest are the results of the tests for resistance to PAS. Again the series is too small to permit conclusions and the series treated with PAS

TABLE 2

The Effect of Combined Treatment With PAS, Streptomycin and Promin on the Emergence of Streptomycin-resistant and of PAS-resistant Tubercle Bacilli

Patient's number	Duration of treatment days*	Resistance to Streptomycin		Resistance to PAS	
		Before treatment	After treatment	Before treatment	After treatment
9	104	▲1.0	▲1.0	Not done	0.072
10	180	1.0	♦1,000	0.072	0.018
11	180	1.0	1.0	Not done	0.004
12	90	Not done	1.0	0.004†	0.004
13	145	1.0	1.0	0.004†	0.004
14††	90	1.0	1.0	0.004	0.004
15§	180	1.0	1.0	0.004	0.004
16§	180	▲1.0	1.0	0.009	0.018
17	97	▲1.0	1.0	0.018	0.018
18	129	1.0	1.0	0.036†	♦4.60

*Streptomycin 0.5 gm. once daily: PAS, 5 to 10 gm. orally in four doses daily; promin 5 gm. intravenously daily for 14 days of each 21-day period.

†Culture obtained three weeks after treatment started.

††PAS discontinued after 90 days. Streptomycin and promin continued for an additional 90 days, at which time a culture was found to be resistant to streptomycin.

§Received no promin.

♦Signifies "greater than."

▲Signifies "less than."

alone (Table 1) is too small for comparison. The data suggest, however, that combined therapy may prevent or delay resistance to PAS. This, of course, can be determined only by studies on much larger groups of patients. Observations on 11 other patients being treated with streptomycin, PAS and promin are not included in Table 2 because none of them have been treated for longer than 60 days. In none of these 11 patients have streptomycin-resistant or PAS-resistant tubercle bacilli been demonstrable.

Comment

The method of detecting PAS-resistant bacilli in our studies was chosen merely because we routinely use egg-yolk agar for streptomycin-resistance studies. We prefer a solid medium because differences in the amount of growth are readily seen and because it is possible to select individual colonies for further examination. We have not made a comparison of the various culture procedures that may be used for studying the in vitro sensitivity of tubercle bacilli to PAS, but obviously such a comparison is needed. A standard procedure should be developed and adopted by various workers in order that comparable data may be secured.

The significance of our findings and those of others that tubercle bacilli with an increased resistance to PAS may occur in patients treated with this compound is not known and must await the results of extensive clinical observations correlated with laboratory studies. It is essential that the sensitivity to PAS be determined for cultures obtained from patients prior to, during and after treatment.

The results of studies on cultures of tubercle bacilli from untreated patients suggest that various strains are sensitive in vitro to a low narrow range of concentration of PAS. If, however, it is eventually found that there is a considerable variation in sensitivity to PAS and that cultures having a certain degree of resistance in vitro are also resistant in vivo, it will be necessary to test cultures from every patient before PAS therapy.

Summary

One hundred and two cultures of human-type tubercle bacilli from patients who had not received PAS were found to be resistant to 0.018 mg. of PAS per 100 ml. of egg-yolk agar but not to 0.072 mg. Four cultures were resistant to 0.072 mg. and one to 0.144 mg. per 100 ml. of the medium. Cultures from four of eight patients treated with PAS alone for prolonged periods (90 to 267 days) were able to resist the inhibitory action of PAS at concentrations greatly in excess of that required to inhibit the growth

of strains from untreated patients. In a group of 10 patients treated with streptomycin, PAS and promin, only one was found after treatment to have streptomycin-resistant tubercle bacilli and one other had PAS-resistant tubercle bacilli.

REFERENCES

1 Youmans, G. P., Williston, Elizabeth H., Feldman, W. H. and Hinshaw, H. C.: "Increase in Resistance of Tubercle Bacilli to Streptomycin: A Preliminary Report," *Proc. Staff Meet., Mayo Clin.*, 21:126, 1946.

2 Lehmann, Jorgen: "Para-aminosalicylic Acid in the Treatment of Tuberculosis," *Lancet*, 1:15, 1946.

3 Youmans, G. P.: "The Effect of Para-aminosalicylic Acid in Vitro and in Vivo on Virulent Human Type Tubercle Bacilli," *Quart. Bull., Northwestern Univ. M. School*, 20:420, 1946.

4 Sievers, Olof: "Experimentella forsok med para-aminosalicylsyra (PAS) och olika slag av bakterier," *Svenska Lakartidningen*, 43:2041, 1946.

5 Youmans, G. P., Raleigh, G. W. and Youmans, Anne S.: "The Tuberculostatic Action of Para-aminosalicylic Acid," *J. Bact.*, 54:409, 1947.

6 Delaude, André, Karlson, A. G., Carr, D. T., Feldman, W. H. and Pfuetze, K. H.: "Increase of Resistance of Tubercle Bacilli to Sodium P-aminosalicylic Acid: Observations on Cultures Isolated from Patients During Chemotherapy," *Proc. Staff. Meet., Mayo Clin.*, 24:341, 1949.

7 Hurni, H.: "Gibt es eine Gewohnung an p-Aminosalicylsaure (PAS)?" *Experientia*, 5:128, 1949.

8 Sievers, Olof: "Sensitivity of Tubercle Bacillus," *Lancet*, 1:798, 1949.

9 Eastlake, Chesmore, Jr. and Barach, A. L.: "Use of Para-aminosalicylic Acid in Chronic Pulmonary Tuberculosis," *Dis. of Chest*, 16:1, 1949.

10 Widstrom, G. and Swedberg, B.: "Undersokningar anaende tuberkelbacillernas virulens och resistens i samband med terapiforsok," *Nord. Med.*, 36:2148, 1947.

11 Widstrom, G. and Swedberg, B.: "Données expérimentales dans la chimiothérapie de la tuberculose," *Le Poumon*, 5:225, 1949.

12 Swedberg, B. and Widstrom, G.: "Treatment of Experimental Tuberculosis in Mice and Guinea-pigs with Para-aminosalicylic Acid (PAS) and Streptomycin," *Acta med. Scandinav.*, 131:116, 1948.

13 Swedberg, B. and Widstrom, G.: "Om samband mellan tuberkelbacillstammarmas resistens in vitro och kemoterapieffekt in vivo," *Nord. Med.*, 40:2227, 1948.

14 Widstrom, G. and Swedberg, B.: "Variationer i kemoresistens has nagra tuberkelbacillstammer," *Nord. Med.*, 40:2225, 1948.

15 Sweany, Henry C.: (Chicago, Illinois), Personal communication.

16 Odelberg, Axel: (Ostersund, Sweden) Personal communication.

17 Dunner, Edward, Brown, W. B. and Wallace, Jack: "The Effect of Combined Streptomycin and PAS on Emergence of Resistance," *Minutes of the Seventh Streptomycin Conference*, Veterans Administration Office, Washington, D. C., pp. 25-28, 1949.

18 Karlson, A. G., Delaude, André M., Feldman, W. H. and Carr, D. T.: "The Effect of P-aminosalicylic Acid (PAS) on Tuberculosis in Guinea Pigs Infected with Tubercle Bacilli Resistant in Vitro to PAS," *Proc. Staff Meet., Mayo Clin.*, 25:544, 1949.

19 Karlson, A. G., Pfuetze, K. H., Carr, D. T., Feldman, W. H. and Hinshaw, H. C.: "The Effect of Combined Therapy with Streptomycin, Para-aminosalicylic Acid and Promin on the Emergence of Streptomycin-resistant Strains of Tubercle Bacilli: A Preliminary Report," *Proc. Staff Meet., Mayo Clin.*, 24:85, 1949.

20 Karlson, A. G. and Needham, G. M.: "Determination of Streptomycin Sensitivity of Tubercle Bacilli by Use of Egg-yolk Agar Medium," *Proc. Staff Meet., Mayo Clin.*, 23:401, 1948.

Cavernostomy and Tamponade of Pulmonary Cavities with Para Aminosalicylic Acid*

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The pulmonary cavity is the *focus* considering the campaign against tuberculosis. The cavity decides the patients fate and dominates the epidemic state of tuberculosis. The persistence of the destructive lesions perpetuates the source of infection.

Of people in whom sputum tubercle bacilli are found, more than 50 per cent die within 10 years of the discovery, in spite of collapse therapy and sanatorium care. This has been so up to the present, and the future will show how much antibiotics and chemo-therapeutics will be able to reduce this alarming mortality.

Streptomycin is generally effective in hyperaemic foci such as specific meningitis, laryngitis, bronchitis and some forms of intestinal tuberculosis. On the other hand, foci whose blood supply is reduced by lical trombosis, such as a caseous lung infiltration or a cavity wall, are as a rule not affected by streptomycin or para-aminosalicylic acid. Ulcerations of the larynx or of the intestines may heal, whereas the lung cavity, which has provoked it, will remain and may cause further disseminations in the lung or elsewhere. A second, even a third course of treatment must then be undertaken which is likely to end with the development either of toxic symptoms in the patient or streptomycin resistance in the tubercle bacillus. Therefore the tuberculous cavity remains the deciding factor in the survival of the patient and the perpetuation of the epidemic state in spite of antibiotics and chemo-therapeutics.

Taking into consideration the reduced permeability of the cavity wall and its poor blood supply, we introduce an adapted procedure. The three essential phases of the method are:

1) The gradual establishment of the cavernostomy by means of laminaria sticks, that is a "stoma" between the skin and the cavity.

2) The regular packing of the cavity with gauze, soaked in streptomycin or P.A.S.

3) The closure of the draining bronchus by means of diathermy, applied through an operating thoracoscope.

The draining bronchi of the cavity are generally open. If they appear to be closed, it is our experience that in active and suppurative cases this closure is fictitious and not a true one in the

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anatomic-pathological sense. It is no question of a real fibrotic obliteration, but the bronchi can be blocked by specific granulation tissue. On this error is based Monaldi's method and it explains its failure.

We tried a "Cavernostomy" the first time at the beginning of 1947 on two cases which had to be considered as lost. The intervention had been carried out with improvised instruments. Both patients are perfectly healthy today. The construction of the definite equipment for the tamponade of lung cavities took a whole year, so that further patients could only be treated since March 1948.

According to the usual resources of tuberculosis therapy out of 38 cases, 30 had to be considered as hopeless. For the 8 others thoracoplasty would have been indicated, but the intervention was refused. The secretion of all the cavities, treated with our method, became and remained free from tubercle bacilli and that on an average of 17 days after the first streptomycin or P.A.S. tamponade. Later, the expectoration became negative if no other destructive foci were present: 28 patients became free from tubercle bacilli in the sputum. The other 10 had been the most desolate cases, yet cavity secretion became negative, but expectoration remained positive. Even these patients have improved in an astonishing way, temperature became normal, symptoms of toxic cardiac disturbances disappeared so much that thoracoplasty or a second cavernostomy on the same or on the contralateral side became possible.

Of course the method was at the beginning purely theoretical and experimental and we had therefore morally no right to try it on patients who had a chance of recovery with the already established therapy. Therefore the modest number of cases. *We had to fear complications from the gradual dilatation of the cavernostomy channel* as a rapid aggravation of the destructive lesion itself, or disseminations, or mortal haemoptosis, all this provoked through the unavoidable traumatisme of the cavity.

Fortunately *no fatal complications* occurred and all the patients are alive today, some of them leading a normal life, and the others have a good prognosis. It is impossible to judge how many of them would be dead by now without our direct treatment of the cavity. To conclude, our method cannot be considered any longer as theoretical and experimental or even dangerous. As clinical findings show, it is a most promising enrichment for treatment of cavitary tuberculosis.

The complications we have to expect are:

1) Hemorrhages are seldom, very seldom alarming and easily

stopped by packing of the bleeding cavity with gauze soaked in Thrombin "Roche."

2) Fresh infiltrations around the cavity with a high but short rise of temperature. In one case lobar pneumonia developed but entirely resorbed in 12 days.

3) In four cases there was severe irritation of the cavity, the trachea and the larynx, provoked by gauze-packing with a soiled preparation of para-aminosalicylic acid. These four patients recovered, the cavities closed and the sputum became negative. But in Dublin a cavernostomy case, on the way to recovery, died in a delay of 48 hours after a tamponade with a bad preparation of P.A.S.

A dangerous run in the international market of P.A.S. has started, serious for patients and bad for the reputation of our method. According to our researches the P.A.S. of Dr. Wander, Berne, the so-called *"Aminacyl"* in a solution of 5 per cent has no noxious influence on lung tissue and yet is highly efficacious. I therefore recommend this preparation of para - aminosalicylic acid. If Aminacyl is not available we better make the gauze-packing with 0.1 gr. streptomycin in 20 cc. of physiological solution. Besides this local application we give 0.5 gr. streptomycin intramuscularly or Aminacyl tablets.

The internal opening of our *big calibre rubber tubes* touches often the cavity wall, which hinder the discharge of pus; even more, through a sucking action we imitate the phenomenon of a cupping glass and irritate the cavity wall or risk hemorrhages. For this reason we recently have not made any draining with sucking action.

While coughing, the cavity pus is thrown out directly into a little waterproof bag, fixed on the tube. In this way we avoid, for the discharge of the cavity secretion, the detour over the bronchial system, we have less poisoning. Bronchial and larynxulcerations have a better chance to heal thanks to this "short-circuit-expectoration" where the cavity tube is acting like a trachea.

Only with gauze-packing does all of the cavity wall get into intimate contact with streptomycin or P.A.S. The repeated instillation of the fluid on the gauze end assures the continuity of the direct application, because the gauze acts like a wick. Practically we imitate in some way the treatment of tubercle bacilli in a test glass and so the revolutionary therapeutic effect finds its explanation, the sterilization of cavities on an average of 17 days.

By regular *cavernoscopy* we are able to follow the improvement as clearly as the healing of tuberculosis in the eye with the ophthalmoscope. After the first few tamponades, the cavity wall

looses its caseous aspect, becomes smooth, has more and more blood supply and becomes highly hyperaemic. The permeability is increasing and so tubercles next to the cavity are now influenced by the sterilizing effect of P.A.S.

The closure of the draining bronchus: Specific granulation tissue of the draining bronchus may be gradually sterilized, then more and more substituted by fibrotic cells and the consequent retraction may finish in a real closure, that is a fibrotic obliteration of the bronchus. This has to be verified by cavernoscopy control, colored liquid and radiological contrast.

If the bronchus does not obliterate, we coagulate its opening with high frequency current (usually several sessions are necessary). A diathermy scurf never detaches but is substituted by fibrotic tissue and again by the consequent retraction we finally obtain the desired obliteration of the bronchus.

The finish of the treatment: Instead of the periodical dilatations of the cavernostomy and repeated tamponades, we let retract the stoma more and more. Once a last and thinnest drain is extracted, the remaining fistula closes at once. The scar left in the skin is not bigger than a pea.

CONCLUSIONS

Therapeutical out-look: Desolate cases may become curable. *Lobectomy for cavitary tuberculosis* without, before or after thoracoplasty, as a rule will be superfluous. Giant cavities or, destructive lesions, badly situated with a view to collapse therapy, shrink by preliminary cavernostomy, so that finally the thoracoplasty becomes possible and efficacious. In the usual indication field of thoracoplasty the plasty may be avoidable in a way that some of these cases recover by an accessory phrenic nerve crush plus pneumoperitoneum, and others by cavernostomy alone. Pregnant women with cavitary tuberculosis may recover and have a healthy baby.

And even more, considering the epidemic aspect, the public health as well as state economy, the method seems to be of value.

CONCLUSIONES

Los casos desesperados pueden convertirse en curables. La lobectomía para la *tuberculosis cavitaria,* sin, antes o después de toracoplastía, como regla será superflua. Las cavernas gigantes o las lesiones destructivas, mal situadas por lo que se refiere al colapso, se reducen por la cavernostomía previa de manera que la toracoplastía finalmente se torna posible y eficaz. En el campo habitual de las indicaciones de la toracoplastía, puede en cierto modo ser evitable ya que ciertos casos se recuperan por una frenopraxis accesoria más neumoperitoneo y otras por la simple cavernostomía.

Las embarazadas con tuberculosis cavitaria pueden recuperarse y dar a luz un producto sano.

Y más aún, considerando el aspecto epidémico, la salubridad pública así como la economía estatal, el método parece ser de valor.

Discussion

WILLIAM A. HUDSON, M.D., F.C.C.P.
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It is a pleasure to discuss Dr. Maurer's approach to the control of tuberculous cavities. There is an old axiom that in treating cavities by drainage the successful procedure must provide the means of continuous and complete removal of secretions from the cavity. Packing the cavity with gauze has proved to be an effective means of providing drainage. The use of medications to aid in sterilizing the cavity need not be limited to any particular drug but any chemical which has the power of destroying the germs present may be used. The sulfa drugs were used effectively before the introduction of penicillin and streptomycin.

In the past I have had most satisfaction through the use of open cavernostomy with the placing of skin flaps on the inner walls to aid in obliterating and lining of the residual defect. Various chemotherapeutic agents have been used to aid in controlling any infection present. The following cases give an indication of the type of cavities which we have treated by open cavernostomy. They range from the giant bilateral apical to the mid-lung cavity in a remaining lung after one lung has been collapsed by thoracoplasty.

One important point that must not be overlooked is the necessity of obtaining closure of all bronchi that open into the cavity before allowing the drainage tract through the skin to close. If the skin opening is allowed to close before the bronchial openings are all closed there is frequently a recurrence of the cavity through reinfection by way of the open bronchus.

I am impressed by the results obtained to date by Dr. Maurer and shall apply the procedure which he has described in selected cases in my own practice. Again I would issue a word of caution. Do not be too hasty in discontinuing the packing of the cavity—be certain all bronchial openings have closed.

I must commend Dr. Maurer on his ingenuity and skill and I would wish for you and me a portion of the patience exhibited by Dr. Maurer in the treatment of his patients.

JOHN V. THOMPSON, M.D., F.C.C.P.
Indianapolis, Indiana

It was a privilege to hear Dr. Maurer's experiences. He should be commended for his early success in converting the sputa in such a group of poor risk patients. The semi-closed method utilizing a large bore tube would seem to present some problems. I should like to ask Dr. Maurer if he has had difficulty with persisting sinuses, fistulae or possibly recurrence of the cavity by this procedure and how he has handled these complications. I have preferred wide open method of cavernostomy.

It should be noted that most of the attempts at open drainage of tuberculous pulmonary cavities reported in the literature were marked by an apparent lack of consideration for the other pulmonary lesions. All cases in the following series were far advanced, bilateral, and of the poor risk type. There were 29 patients in the series under consideration upon whom 31 pneumonotomies were performed. Twenty-four were operated on from two to seven years ago, and all followed to date. Seventeen had a recurrent, new or residual cavity beneath apparent maximum thoracoplasty. Seven patients had a recurrent or residual cavity where thoracoplasty was not maximum, but could not be extended because of bronchial disease; contralateral collapse; unstable contralateral lesion; and other complications. Five had isolated lower lobe cavities over diaphragmatic paralysis.

It would appear that other pulmonary tuberculous lesions, particularly in the regions adjacent to the cavity, probably should be relatively stable or have good possibilities of control. The trauma incident to operation and the contraction of fibrous tissue in obliterating the healing cavity must affect the adjacent lung areas biologically as well as mechanically. In all the patients of this series the lesions adjacent to the cavitation had been brought under at least the partial effect of some collapse procedure.

It was observed that the more widely the cavity was opened to the exterior without cutting excessively into lung tissue, the better it appeared to heal and obliterate. The medial cavity wall was coagulated to destroy it as much as possible. A large skin flap was dissected up superiorly or laterally and the free end sutured to the cavity wall or pleura. These flaps appeared later to keep the wound open and also acted as a point from which epithelization took place over the deeper parts of the wound. Likewise the medial or inferior edge of the skin was sutured to the muscles. The wounds were loosely packed open with gauze.

Recently three cases with tension cavities present were approached in a somewhat different manner. The cavity wall was merely slit open and a skin flap sutured to the cavity wall to act

as a ball valve drainage somewhat similar to the Eloesser flap operation for empyema. These cavities were not packed with gauze. It does not appear that this type of drainage is going to be as satisfactory as the wide open type of exteriorization described above.

The postoperative care consists of a long period of daily light packing with gauze which may be soaked alternately in penicillin, streptomycin, tyrothricin or cod liver oil to keep the wound as clean as possible. Occasional stimulation of the granulations and bronchial fistulae with silver nitrate or the cautery is beneficial. Recently dusting of the depths of the wound with P.A.S. has been done. There has been no remarkable change as a result of this dusting but the wounds do appear somewhat cleaner.

After about nine months of such management, if the wounds do not show signs of becoming healed in the near future, a plastic closure of the defect may be considered. There is apparently too much active infection present to attempt closure before this time in our experience. The wound is prepared for several days with wet dressings and antibiotics are administered and continued postoperatively. A plane of cleavage is established between the granulation tissue and the underlying tissues and the former is bluntly dissected out of the defect. The defect is then obliterated by reapproximating the tissues in layers with chromic c. If a bronchial fistula is present, in addition a pedicled muscle graft is obtained from the adjacent musculature and sutured into the orifice of the bronchus.

Ten plastic closures of sinuses and fistulae were performed. Eight healed promptly and two broke down but later healed. Of the 24 patients followed for over two years, 17 have healed wounds. Seven of which healed spontaneously and 10 were closed by plastic procedures. Three patients have persistent complicated sinuses which might heal spontaneously but will probably require further operative procedures. Four patients are dead. Five recent cases appear to be healing satisfactorily, but have not reached the point yet where the decision between operative closure and spontaneous healing can be made.

Of the 25 living patients in the entire series sputum conversion took place in all. However, three have developed positive sputum again from the appearance of cavitation in the contralateral lung. *Seventy-five per cent* of the patients operated on over two years ago have both negative sputum and healed wound. Excluding the recent cases, all living patients are now working except the three with positive sputum, and two of whom are about to be discharged from the hospital.

One patient, after three years, died of a complicating tuberculous spine; another patient succumbed to a general breakdown of the

tuberculous process; the third patient died from pneumonia after cavernostomy for a cavity in the contralateral lung performed by another surgeon. The other death was caused by an embolism while the patient was undergoing cauterization of a persistent sinus. Mortality thus for the entire series was 13 per cent to-date.

The Treatment of Tuberculosis in Sweden with Para-Aminosalicylic Acid (PAS): A Review

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Historial Remarks

The tuuberculostatic effect of PAS was discovered by the writer in 1943.[1-3] On the basis of the studies of F. Bernheim on the stim ulating effect of benzoic and salicylic acids on the respiration of the tubercle bacillus, it was suggested that the introduction of an aminogroup in the salicylic acid molecule in para-position (4-position) should be able to convert the stimulating effect into an inhibitory effect and thereby inhibit even the growth of the bacillus. PAS was synthesized by K. G. Rosdahl at the Ferrosan Company in Malmo, Sweden, in December 1943 and the tuberculostatic effect demonstrated in vitro in the same month.

The first clinical trials were conducted by Dr. G. Vallentin and the writer at Renstroms sanatorium in Gothenburg in March 1944, thus about half a year before the first clinical trials with streptomycin in the United States.

PAS was first used in the local treatment of Monaldi fistulas and abscesses, then in hopeless cases of pulmonary tuberculosis and later on in moderate and slight cases (Lehmann[1] and Vallentin[4]). During the following years the Ferrosan Company produced larger quantities of PAS and a team work on the treatment of pulmonary tuberculosis in six Swedish sanatoria was established. A report on this work—378 cases—was presented at the conference of the Scandinavian Tuberculosis Association in Copenhagen in 1948. (Vallentin, Tornell, Beskow, Carstensen, Thune, Helleberg and Lehmann[5]).

Chemical Properties, Absorption, Excretion and Toxicity of PAS

PAS is an acid of about the same strength as benzoic acid. It is soluble in water only to 0.2 per cent. The sodium salt is however soluble to about 96 per cent (Rosdahl[6]). The solubility decreases with decreasing pH. These data are of interest for the absorption of PAS: because of the slight solubility in acid solution it will only to a slight extent be absorbed in the stomach. When successively neutralized in the intestines PAS is dissolved and absorbed. PAS is a small molecule and is quickly absorbed and

*From the Central Laboratory, Sahlgrens Hospital, Gothenburg, Sweden.

excreted. A peroral dose of 4 g. of the acid will be excreted within three to four hours, the sodium salt somewhat quicker.

The blood concentration is naturally dependent on the speed of absorption and the speed of excretion and will have its maximum after ½ to 1 hour. In order to delay the absorption of PAS the Sewdish preparation of PAS* is enteric coated in small granules first dissolving in the small intestines. With this preparation the blood will show maximum values first after about two hours and after five to six hours a single dose of four grams is excreted in the urine. Repeated doses with an interval of three to five hours is required for a permanent blood concentration.

High concentrations of PAS are achieved in the kidney and the urine. A daily dose of 14 grams PAS granules (11 grams PAS*) will give a concentration of 300 to 900 mg. per cent in the 24 hours urine. As such high concentrations are not necessary for the treatment of tuberculosis of the kidney and urinary tract the treatment of these forms of tuberculosis can be done with a lower dose (8 to 10 grams granules).

About half of the PAS in the urine is found in the acetylated form which is not tuberculostatic. The PAS not excreted is mainly found in the tissues rich in elastin (Alin and Helander[7]). Due to the high solubility of the PAS in the urine no deposits of PAS are seen in the kidney or urine even after the highest dosage of PAS (20 to 30 gm. sodium-PAS per day). See also Alin and Difs.[8]

As to the *toxicity* of PAS no damage of the liver, heart or kidney have been seen. Intestinal complaints in the form of nausea, vomiting and diarrhea was frequently seen before a suitable coating substance was found. Still some sensitive patients react in this way. However, after a free interval of four to six days the drug is often tolerated well.

Administration of PAS

Different forms of administration of PAS have been tried: Permanent *intravenous* infusions (2 per cent) in most cases give rise to trombophlebitis within three to four days. This experience was won with rather impure preparations and possibly the more pure preparations of recent years are better tolerated. *Intramuscular* injections have to be given in large repeated doses (10 ml., 10 per cent solution) in order to provide permanent blood concentrations. As they are rather painful and PAS is too quickly absorbed and excreted, this form of administration cannot be recommended. The *peroral* administration is to be used as the routine method.

*The granules contain 30 per cent coating substances. Special measures have been used containing ca. 2.2 grams of the granules. That is why the doses refer to the granules. In the future measures containing 2 grams of the acid will be used.—The Ferrosan LTD. Malmo 3. Sweden.

Intestinal complaints can be treated with interruption of the administration or a few drops of opiate or a teaspoonful of magnesium oxide before PAS is given. *PAS should always be given together with or after a meal* or a glass of milk and some bread and butter. The granules or dragées should not be chewed.

Intralumbar injections of 5 to 10 per cent sodium PAS solutions have been used in cases of meningitis (two times a week in the beginning of the disease). After a few weeks treatment the viscosity of the cerebrospinal fluid increases and makes aspiration impossible—if due to the disease or the injections has not been recognized.

Intrapleural injections have been used in the treatment of empyema. During the first year 200 to 300 ml. 5 per cent solutions were used but later on only 20 to 25 ml. 10 to 20 per cent solutions were injected after aspiration once a week according to Dempsey and Logg.[9]

For the *local application* of PAS solutions in the treatment of skin-tuberculosis (lupus), fistulas and abscesses 5 to 10 per cent solutions have been used. For the use in fistulas and abscesses the viscosity of the solutions was increased as desired by addition of 1 to 2.5 per cent cellugelphosphate. PAS in ointments has not been effective (Lemming[10]).

Pulmonary Tuberculosis: A Comparison with Streptomycin

The greatest experience of the treatment with PAS has been gained in pulmonary tuberculosis. In the following an attempt is made to compare the efficacy of PAS as evidenced from the above mentioned team work of six Swedish sanatoria (Vallentin, Tornell, Beskow, Carstensen, Thune, Helleberg and Lehmann[5]) with that of streptomycin as presented by the Army, Navy and Veterans Administration in the *American Review of Tuberculosis,* 56:485, 1947.

The PAS material consisted of 378 cases of pulmonary tuberculosis. Certain rules were established for the selection of the cases and the treatment. The rules were the following:

1) The diagnosis should be made by a positive culture or guinea pig test just before the treatment or by a typical x-ray together with a positive slide.

2) The pulmonary process should be progressive or stationary for some months without signs of regression.

3) Preferably far advanced and moderate cases of exudative as well as proliferative types with or without other complicating localizations of tuberculosis should be treated.

4) The observation time before treatment should be at least two months with rest in bed and ordinary sanatorium regime.

5) Cases treated with collapse therapy were included in the material and not considered to interfere with the estimation of the PAS effect, if the collapse therapy had been finished three months before the PAS treatment was commenced or the collapse therapy had been instituted three months before PAS and the process still showed signs of progression. The collapse therapy should be continued during the treatment as before PAS. No form of collapse therapy should be introduced during the PAS treatment or during the observation time after PAS.

6) The age of the patients should be between 15 and 60 years, preferably between 15 and 35 years.

7) PAS should be given orally with an average dose of 14 gms. a day divided into four to six doses. The treatment should be continued at least during one month and if possible without interruption.

8) The observation time after PAS should be at least three months.

9) Certain rules were established for laboratory procedures including erythrocyte sedimentation rate once a week, hemoglobin and count of the white cells every 14 days and sputum examinations and x-ray every month. The patients were weighed once a week or once fortnightly.

TABLE 1

Clinical Material

	SEX				AGE IN YEARS					
	Male		Female		5-15 0 - 0		15-35 18-30		35 31-50	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
PAS material	99	(48.3)	106	(51.7)	6	(2.9)	151	(73.7)	48	(23.4)
Streptomycin material	219	(98.2)	4	(1.8)	0	(0)	161	(72.2)	62	(27.8)

	Extent of Lesion						Predominant Type of Lesion			
	Minimum		Moderate		Far. Adv.		Exudative		Proliferative	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
PAS material	10	(5)	41	(20)	154	(75)	122	(59.5)	83	(40.5)
Streptomycin material	2	(0.9)	65	(29.1)	156	(70)	83	(63.4)	48	(36.6)

	CAVITIES				COURSE OF DISEASE			
	Present		Not Present		Progressive		Stationary	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
PAS material	169	(82.4)	436	(17.6)	184	(89.7)	39	(10.3)
Streptomycin material	182	(81.6)	41	(18.4)	122	(85.5)	19	(14.5)

The experience was soon gained that it was not always possible to maintain an observation time of two months before the treatment with PAS. Rapid deterioration of the patient during the observation time as well as the claims of the patients or their relatives called for earlier treatment. The rules established were fulfilled in only 205 cases. This "selected material" is therefore best adapted for elucidating the therapeutic effect of PAS. No collapse therapy was thus *instituted* during the observation time before the PAS treatment, during the treatment or during the after-observation time.

The streptomycin material included 223 cases. Collapse therapy was in this material used in some cases during chemotherapy when a contralateral spread appeared or during the afterobservation time if it was found "essential" to the patient. No figure is given of the frequency of such collapse therapy. It is therefore ques-

TABLE 2

Frequency of Complicating Tuberculous Localizations in Pulmonary Tuberculosis. Total material, 378 cases; Selected material, 205 cases.

	Total Number		Selected Material	
	No.	Pct.	No.	Pct.
Tuberculous laryngis	9	(2.4)	7	(3.4)
Tuberculous tracheobronchial	35	(9.0)	30	(14.6)
Pleurit, exs.	18	(5.0)	7	(3.4)
Empyema pleurae	29	(7.7)	22	(10.7)
Tuberculous intest.	55	(14.5)	49	(23.9)
Tuberculous urogenital.	10	(2.7)	8	(4.0)
Tuberculous lymfoglandul.	8	(2.1)	7	(3.4)
Tuberculous ossium and art.	5	(1.3)	3	(1.5)
Tuberculous miliary	4	(1.1)	4	(2.0)
Tuberculous pericarditis	2	(0.5)	1	(0.5)

TABLE 3

Treatment

Duration of PAS Treatment, in Months

	1		1 to 3		3 to 6		6	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
PAS material	0	(0)	62	(33.3)	100	(48.8)	43	(20.9)
Streptomycin material:	Four months' treatment. Daily dose generally 1.8 gm.							

tionable whether the streptomycin material should be compared with the "total" PAS material or the "selected." However to exclude too many interfering undefined factors from the PAS material, the "selected" has been chosen for the comparison. In order to compare it with the streptomycin material it was necessary to rearrange the material according to the American classifications. However, some of the grouping differed too much in the two materials to allow a direct comparison and the evaluation of the treatments have to be described for each material.

When reviewing the two *clinical materials* (Table 1) it is astonishing to find that they are comparable in many respects: age of patients, character of the pulmonary processes, frequency of cavities and so on. The observation time before treatment is two months in both materials. The impression has, however, been gained that the cases in the "far advanced" group in the PAS material are more severe than in the streptomycin material. This is evidenced by the high frequency of complicating localizations of tuberculosis—especially that of intestinal tuberculosis (Table 2). Thus there should not be expected as good results in the PAS material as in the streptomycin material.

The treatment with streptomycin was fixed to four months whereas the PAS treatment was adjusted according to the individual cases. As seen from Table 3 the PAS treatment was three to six months in 49 per cent—thus of a similar duration as in the streptomycin material. In 30 per cent the PAS treatment was one to three months and in 21 per cent more than six months.

In spite of the differences in the duration of the treatment the comparison of the efficacy of the two drugs seems justified, as the majority of the cases in the streptomycin material—about 80 per cent—had developed resistance to the drug within three to four months treatment. Therefore, only in a minor number of the cases further improvement could be expected to take place by continued treatment.

In the treatment with PAS the problem of bacillary resistance is of less clinical importance as, to our present experience, it develops in a minor part of the cases, is less pronounced and coming first after three to five months treatment (Lehmann[11]). Some cases have been treated one to two years without developing resistance. However, even in a minor part of this material better results could possibly have been attained, as part of the cases were not adequately treated due to lack of PAS during the first year. Summing up, it seems as if the two materials to the same degree will present results indicating what can be achieved by the two drugs.

As to the *clinical observations during treatment* the PAS mater-

ial shows better results in *temperature and sedimentation rate* (Table 4).

Normal temperature was attained in 75 per cent with PAS, in 47 per cent with streptomycin. A "decrease" in E.S.R. was observed in 84 per cent with PAS, in 30 per cent to normal values, whereas a "decrease" in the streptomycin material was registered only in

TABLE 4

Clinical Observations During PAS Treatment

	TEMPERATURE						GAIN IN WEIGHT	
	Afebrile throughout		Decrease to normal		No decrease to normal		Unaffected	1 kg or more for the PAS material
	No.	Pct.	No.	Pct.	No.	Pct.	No. Pct.	No. Pct.
PAS material	53	(25.9)	114	(75)	19	(12.5)	19 (12.5)	127 (61.9)
Streptomycin material	63	(28.2)	76	(47.5)	41	(25.6)	43 (26.9)	188 (84.3)

	ERYTHROCYTE SEDIMENTATION RATE					
	Normal throughout		Decrease		Unaffected	
	No.	Pct.	No.	Pct.	No.	Pct.
PAS material	10	(4.9)	161	(83.7)	34	(16.3)
Streptomycin material	39	(17.5)	94	(51.1)	90	(48.9)

	SPUTUM				BACILLI IN SPUTUM OR LAVAGE					
	Not present		Disappearance or decrease		Not present before treatment			Present before Treatment		
					Continued negative		Changed positive	Changed negative		Continued positive
	No.	Pct.	No.	Pct.	No.	Pct.	No. Pct.	No.	Pct.	No. Pct.
PAS material	18	(8.8)	132	(70.5)	0	(0)	0 (0)	58	(28.2)	147 (71.8)
Streptomycin material	?	(?)	178	(79.8)	?	(?)	? (?)	82	(43.0)	108 (57.0)

	X-RAY OBSERVATIONS. PARENCHYMATOUS INFILTRATIONS									
	Complete regression		Marked regression		Moder. or slight regr.			Unchanged		Progress. or new infiltr.
	No.	Pct.	No.	Pct.	No.	Pct.		No.	Pct.	No. Pct.
PAS material	0	(0)	73	(35.5)	60	(29.3)		56	(27.3)	16 (7.8)
Streptomycin material	6	(2.8)	123	(56.9)	54	(25.0)		14	(6.5)	19 (8.8)

	X-RAY OBSERVATIONS. CAVITIES							
	Closed or lost to view		Smaller		Unchanged		Larger or develop. during treatment	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
PAS material	31	(18.3)	46	(27.2)	80	(47.3)	12	(7.2)
Streptomycin material	47	(25.8)	67	(36.8)	68	(37.4)	0	(0)

51 per cent. The *gain in weight* was superior in the streptomycin material, 84 per cent compared with 62 per cent for PAS. However, it is not mentioned how large the gain in weight should be in the streptomycin material to be registered. In the PAS material it was at least one kg.

Concerning observations in *sputum decrease* and *sputum conversion* the streptomycin material is superior. Sputum decrease was observed in 79 per cent as compared with 70 per cent for PAS. Still more striking is the difference in sputum conversion: 43 per cent and 28 per cent respectively. However, here the frequency of the severe cases in the PAS material with old cavities and processes of proliferative type has to be considered. In the less severe "total" PAS material the conversion of sputum was 43 per cent. To some part these better results in the streptomycin material are assumingly due to the use of collapse therapy in this material.

Regressions of *parenchymatious infiltrations* and *cavities* are difficult to compare in the two materials as the figures for the streptomycin material only refers to lesions of the exudative type whereas the PAS material refers to both lesions of exudative and proliferative nature and these were of about the same frequency. Even the classifications of the regressions were different in the two materials. More comparable is the frequency of "progressions or new lesions" during treatment and this is 7.8 per cent for PAS and 8.8 per cent for streptomycin. When studying the streptomycin paper and comparing the different reports with the PAS material it seems, however, as if streptomycin gives somewhat faster and more complete regressions of the infiltrations than PAS. Further studies on more comparable materials, or with more comparable registrations, are necessary for definite conclusions.

Concerning changes in cavities in the two groups there are not too marked differences. "Closure or lost to view" dominates with 23.8 per cent in the streptomycin material as compared with 18.3 per cent in the PAS material.

TABLE 5

After Treatment Observations. Observation Time 3 Months or More

	Improvement continued No. Pct.	Improvement stationary No. Pct.	Worse No. Pct.	Dead. during treat. or after observ. time No. Pct.
PAS material	30 (57.6)	7 (13.5)	7 (13.5)	8 (15.4)
Streptomycin material	77 (34.5)	86 (38.5)	32 (16.4)	? (?)

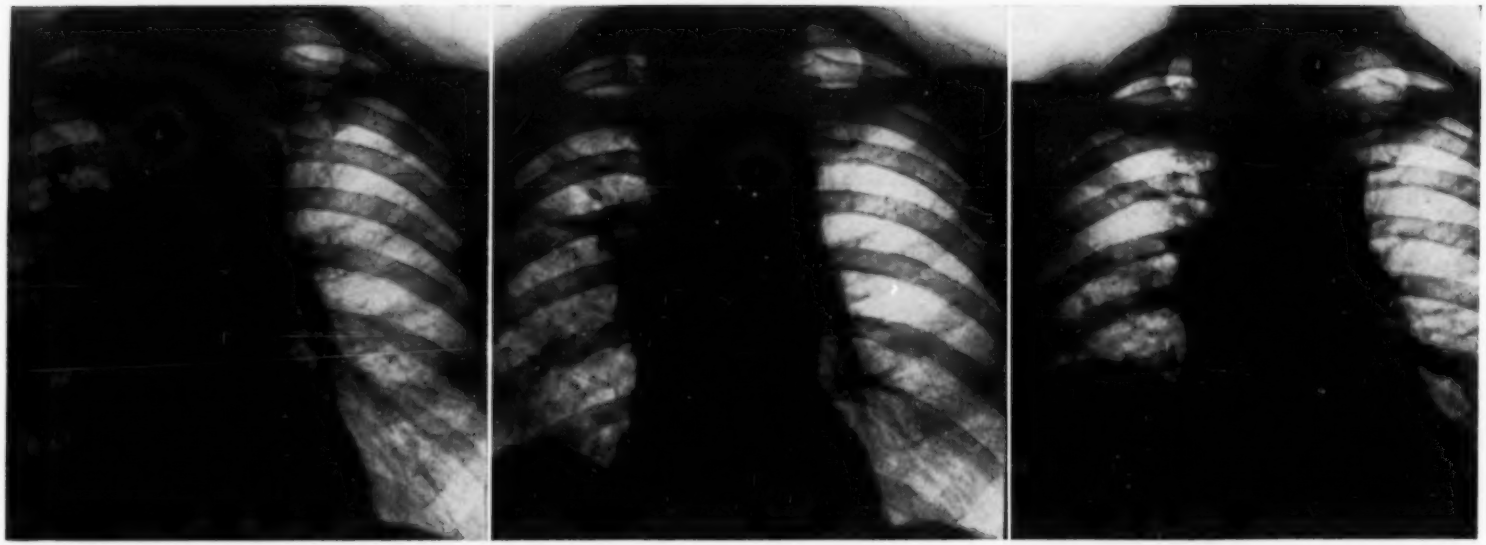

FIGURE 1 FIGURE 2 FIGURE 3

Fig. 1: A man of 62 years. Onset of disease November 1948. Fever, sedimentation rate 50mm/one hour/Westergren, sputum positive, weight 66 kg. X-ray just before treatment December 27, 1948: Right hilus enlarged with a walnut sized ring formed shadow. Scattered infiltrations of the lung field with another walnut sized thin walled ring shadow medial at the right of the clavicle.—*Fig. 2:* The same case on January 28, 1949 after one months treatment with 14 grams PAS granules a day. Normal temperature, sedimentation rate, 6 mm./one hour. Clearing of the infiltrative lesions in the lung field and of the walls of the cavities. Shrinking of cavities.—*Fig. 3:* Same on June 28, 1949 after continued PAS therapy for six months. Cavities lost to view and lung fields nearly cleared of infiltrations. Sputum negative on guinea pig innoculation. Left hospital June 30, 1949 with a gain in weight of 10 kg.

As an illustration of the changes seen on the x-ray films, two cases should be mentioned (See Figures 1-6).

In the *after-treatment observations* (Table 5) the PAS material predominates with a much higher frequency of *continued improvement*—the figures are 58 per cent to 35 per cent for streptomycin. This could possibly be expected as the majority of the bacilli during the streptomycin treatment develope resistance to the drug, whereas this is not the case with PAS. Naturally differences in the judgment of the cases can be responsible to some extent for the different figures.

As to the *deaths,* the frequency in the PAS material is 15.5 per cent. In the single reports on the streptomycin treatment deaths are mentioned, but the total is not given in the leading article.

Recently Bachman, Birath, Karth, Lemming, Lindgren and Lundquist presented another team work on pulmonary tuberculosis.[12]

When comparing PAS and streptomycin attention has to be paid to other properties of the two drugs which have not been registered in the tables, and these are:

1) The frequency with which drug resistance is developed during treatment.
2) The mode of administration, and
3) The toxicity of the drugs.

The daily intramuscular injections of streptomycin is a draw back for this treatment and still more this is the case with the toxic reactions involving the nervous system, which restricts the use of streptomycin in minimal lesions, thus just in those phases of the disease, in which a chemotherapeutic agent has the greatest possibilities. There was a high frequency of drug resistance in the treatment with streptomycin—in 80 per cent of the cases the bacilli were found resistant after three months treatment. With PAS we have only found a slight resistance in a minor part of the cases and it is developed only after several months of treatment.

As a *general conclusion* of this comparison between the two drugs, it must be said that their effect on the symptoms are somewhat different, the streptomycin appearing to dominate in the x-ray findings whereas PAS dominates in its effects on temperature and sedimentation rate and seems to give more stable after-treatment results. The lack of toxemic reactions when using PAS as compared with streptomycin is to the benefit of the former drug and allows us for the first time to treat even early and slight cases of all forms of tuberculosis chemotherapeutically, possibly even out-door patients.

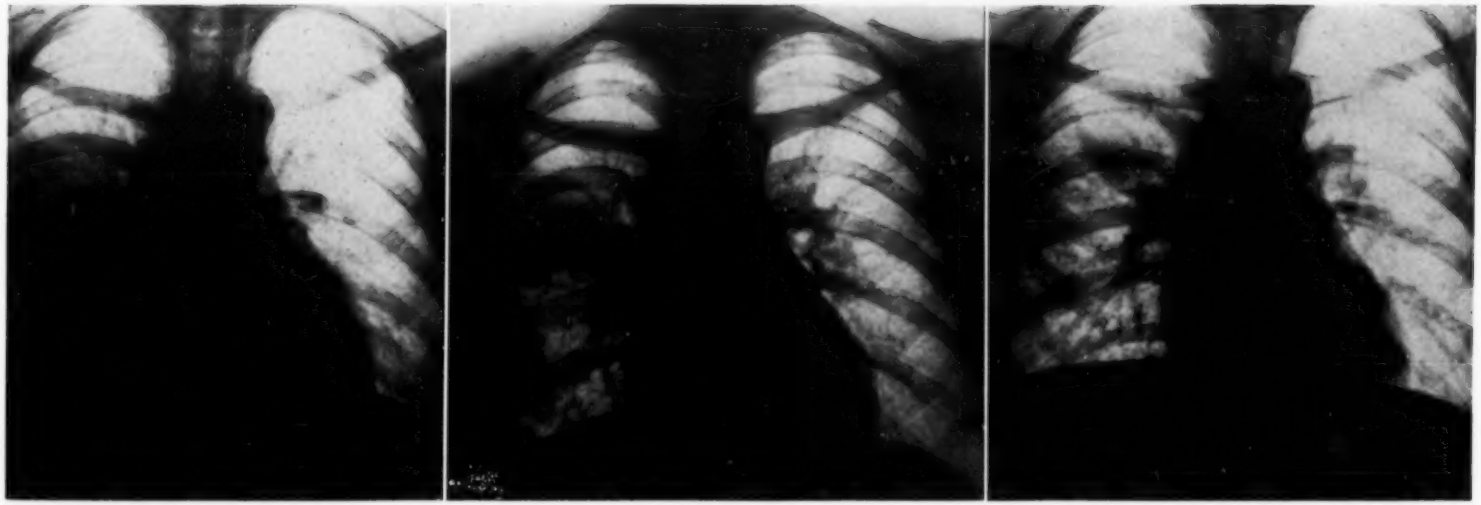

FIGURE 4 FIGURE 5 FIGURE 6

Fig. 4: A woman of 24 years. Acute onset of disease June 1944, ordinary sanatorium regime to November 1945 when she had an acute spread in the right lung with high fever, sputum positive (slide). X-ray November 13, 1945 before treatment: Diffuse infiltration of the right middle and lower part of the lung. PAS instituted November 15 in a dose of 14 grams PAS granules a day and continued to March 27, 1946.—*Fig. 5:* The same case on December 12, 1945. Afebrile. X-ray shows considerable clearing of the lung field, especially the lower part.—*Fig. 6:* The same on March 19, 1946. Continued clearing of the infiltrations in the middle part of the lung. Sputum still positive (guinea pig). In May she had a relapse on the right side with a cavity of walnut size. She responded favorably on retreatment with PAS and left the hospital February 4, 1949, sputum negative, and has since had no relapse.

Tracheo-bronchial Tuberculosis:

At several meetings of the Swedish Tuberculosis Association during the past years cases of tracheo-bronchial tuberculosis—including laryngitis—treated with PAS have been presented. Carstensen especially has stressed the striking effect of PAS in these cases and in all forms of tuberculosis in the mucous membranes. Vallentin has also reported more cases with a good effect. von Rosen has compared streptomycin with PAS treatment using aerosols and has seen good effect of streptomycin but no effect of PAS. The failing effect of PAS in aerosols could be anticipated as it is absorbed too quickly from the mucous membranes to produce any therapeutic effect even if given three times a day as inhalations during 15 minutes.

Intestinal Tuberculosis:

The most dramatic effects of PAS in the treatment of tuberculosis has been achieved in cases of intestinal tuberculosis as reported by Carstensen and Sjolin.[13] The material consisted of 22 cases of pulmonary tuberculosis complicated with intestinal localizations, verified by x-ray in 21 cases and postmortem in the 22nd. Twenty of the 22 cases had exudative cavernous pulmonary lesions, all with bacilli in sputum. In the other two cases the pulmonary process was predominantly of a nodose type and rather stationary. Most of the patients (20) had abdominal pains continuously, tenderness in the right iliac fossa and diarrhea, high temperature and sedimentation rate. All patients were seriously ill and the prognosis considered doubtfull or unfavorable—in some cases hopeless.

Before the PAS treatment the patients had been hospitalized for five to seven months and all forms of treatment tried without success.

The *treatment with PAS* was continued for three to 15 months and was often started over again in connection with performed operations. PAS was given in periods of three to six weeks with free intervals of about a week. The dosage varied from 6 to 14 grams PAS granules a day and was given by mouth in four to six doses. A dosage of 14 grams was generally used but in some cases not tolerated and the treatment therefore often commenced with a lower dose (6, 8 or 10 gms).

The *effect of the treatment* was in the most striking way evidenced by the improvement of the *intestinal symptoms*. All the patients were nearly or completely freed from their abdominal complaints within two to four weeks. The severe diarrhea, refractory against constipating drugs, ceased and so did the often unbearable pains. After-treatment barium enemas showed roent-

genographic improvement in five cases out of the examined 11 patients with total regression in two. In one case with fatal issue the necropsy proved that the intestinal process was in a healing phase.

The effect of PAS on the *general condition, temperature, sedimentation rate* and *weight* was in several cases even more pronounced than in cases of pulmonary tuberculosis. In 15 the weight increased 1 to 23 kg., simultaneously with the general well-being. In seven cases it remained unchanged or decreased. The temperature became normal in 15 out of the 19 patients who were afebrile, while the other four showed only initial or incomplete fall of the temperature. In 11 cases the sedimentation rate became normal. In cases, where the temperature and sedimentation rate remained high, far advanced and progressive lesions of the lungs were present. There was a rather rapid increase in the hemoglobin, when low before treatment.

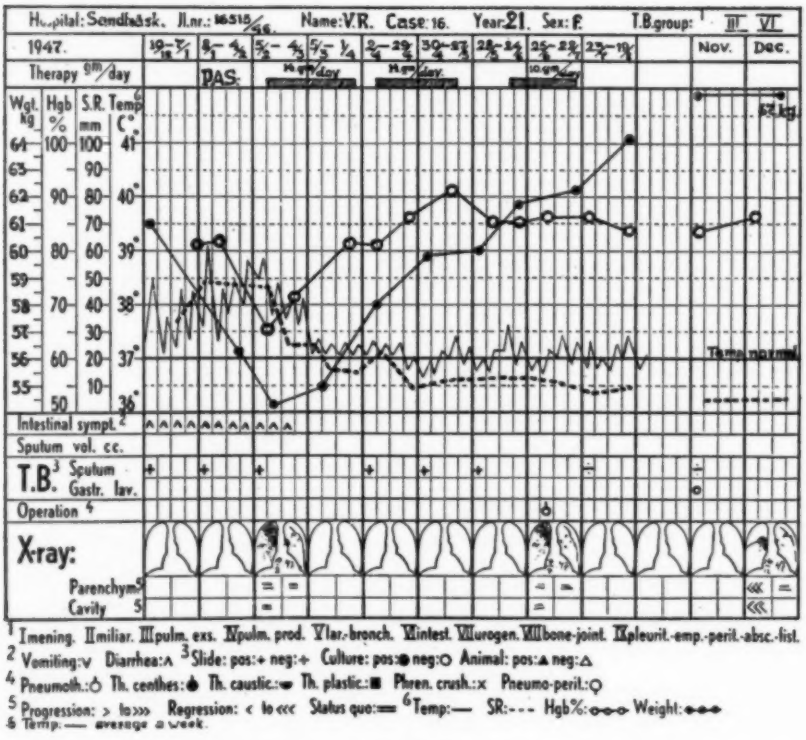
Hospital: Sandhåsk. Jl.nr.: 16515/46. Name: V.R. Case: 16. Year: 21. Sex: f. T.B.group: I II III IV V VI
1947.
Nov.
Dec.
Therapy gm/day
PAS
Wgt. Kg.
Hgb %
S.R. mm
Temp. C°
Intestinal sympt.
Sputum vol. cc.
T.B. Sputum
Gastr. lav.
Operation
X-ray:
Parenchym.
Cavity
Temp. normal
I meningeal. II miliar. III pulm. exs. IV pulm. prod. V lar.-bronch. VI intest. VII urogen. VIII bone-joint. IX pleurit.-emp.-perit.-absc.-fist.
Vomiting: v Diarrhea: ∧ Slide: pos: + neg: ÷ Culture: pos: ● neg: ○ Animal: pos: ▲ neg: △
Pneumoth.: ◊ Th. centhes: ◆ Th. caustic: ▬ Th. plastic: ■ Phren. crush.: x Pneumo-peril.: ○
Progression: > to »» Regression: < to «« Status quo: = Temp: — SR: --- Hgb%: ○-○-○ Weight: ●-●-●
Temp: — average a week.

FIGURE 7: Case of pulmonary tuberculosis complicated with intestinal tuberculosis. Observe the high fever during nine weeks before treatment accompanied with a sharp drop in body weight and hemoglobin. After the institution of PAS the fever decreased and is nearly normal after three weeks and the sedimentation rate follows the drop in temperature down to normal values. The diarrheas disappear after two to three weeks treatment and the body weight and hemoglobin respond with a dramatic increase. After *Carstensen and Sjolin.*

As to the *pulmonary lesions* there was observed roentgenographic regressions in eight cases having fresh exudative processes. In two it was possible to institute pneumothorax and five have undergone successful thoracoplasties.

Of the 22 cases treated, 19 improved, three became worse, and one of them died.

In order to visualize the changes during treatment one of Carstensens and Sjolins cases should be mentioned—a female, born 1926.

Pulmonary tuberculosis was diagnosed in November 1944: exudative cloudy lesions in the left middle lobe and fibrotic, nodose processes all over the right upper lobe. Thereafter the patient was treated at several sanatoria and admitted to Sandtrask in July 1945. Left pneumothorax was instituted in December 1945. Thereafter the lung lesion remained on the whole unchanged until November 1946, when some progress with a small cavity in the right apex was observed. Since November 1946 also abdominal symptoms with pains, diarrhoea, tenderness in the cecal region, high, remittent temperature (the patient was previously afebrile), loss of weight, high sedimentation rate. *Barium enema in February 1947:* Pronounced changes in the cecal region. *PAS treatment was started on February 10, 1947.* There was immediate improvement and the abdominal symptoms completely stopped after 10 to 14 days, the general condition quickly improved (Fig. 7). The lung lesion remained on the whole unchanged with the small right apical cavity and bacilli in the sputum. Right pneumothorax was instituted on July 9 with good results. After pneumothorax the sputum converted to negative. *Barium enema on October 3, 1947* showed marked regression. The patient was discharged from the sanatorium in January 1948. She was in an excellent condition, had no symptom and was able to start work.

Another similar investigation on about 20 cases of intestinal tuberculosis was presented at the Nordiske Tuberkulose lagekongress in Helsingfors, 1949 by Kallquist.[14] The results were in full agreement with the above mentioned.

Encephalo-meningeal Tuberculosis:

The experience in the treatment of these forms of tuberculosis with PAS is rather limited because of their low frequency in Sweden. The writer has treated six cases, none of them living after one year. There is generally seen initial improvement and the patients have been kept alive for weeks or months. In a few cases death suddenly occurred during improvement, assumingly due to hydrocephalus internus, the presence of which was verified by necropsy. Microscopic examination showed that the processes in the brain and the meningeas were in a healing phase with fibrotic envolvement of the aqueductus leading to the hydrocephalus.

PAS was in the first cases given as a permanent intravenous 2 per cent infusion with a total dose of 20 to 30 gm. PAS in 24 hours. However, thrombophlebitis occurred regularly after three

to five days. In other cases peroral administration of the sodium salt-enteric coated in small granules—was used in the same dosage. Intestinal complaint (diarrhea) developed after using 30 grams per 24 hours. In two cases a 2 per cent PAS solution was given by duodenal tube instead of intravenously and high blood concentrations (20 to 25 mg. per cent) were found with values of 10 to 12 mg. per cent in the cerebrospinal fluid. Usually the concentration in the cerebrospinal fluid is one-third to one-fourth of the blood concentration. Therefore the unsatisfactory results in the treatment of encephalo-meningeal tuberculosis is not due to unsatisfactory penetration of the cerebrospinal barrier but rather to a low solubility of PAS in the brain tissue. Treatment of this disease with PAS alone can thus not be recommended. Combined therapy with shorter periods of streptomycin treatment together with permanent PAS therapy has been successful (Carstensen and Soderhjelm[15]).

Miliary Tuberculosis:

Miliary tuberculosis has reacted better on PAS treatment than encephalo-meningitis. In the mentioned team work on pulmonary tuberculosis four cases of miliary tuberculosis (from Renstroms Hospital) were included. In the Childrens Hospital in Gothenburg a few cases have been successfully treated (Y. Akerrhén and the writer) without relapses after one to one and one-half years. A detailed description of these cases has not yet been published. Combined therapy with streptomycin has been more successful than PAS or streptomycin alone (Carstensen and Soderhjelm).

Tuberculosis of the Kidney and Urinary Tract:

About 60 cases of urogenital tuberculosis have been treated by E. Ljunggren and O. Obrant at Sahlgrens Hospital in Gothenburg and at the Ravlanda sanatorium, connected to the hospital as a specialized ward for these cases and in charge of Dr. Ljunggren. Preliminary reports on kidney tuberculosis (Ljunggren[16]) have been presented, from which the following data are collected. In many of the cases combined chemotherapy with PAS, calciferol, streptomycin, chaumogra oil or TB I has been used. As these cases are unsuitable for elucidating the therapeutic effect of PAS they are not mentioned here. In other cases the treatment could not be continued for a sufficient length of time due to social or economical factors. Therefore, only cases being under the treatment, ward and observation for more than one year will be mentioned.

None of the cases had active pulmonary tuberculosis. The examination of the patients included analysis of the urine for tubercle bacilli (culture and guinea pig tests) once a month and in men

even examination of seminal fluid or prostate secretion if negative in the urine, non-protein nitrogen, urine cast and urea clearance. Intravenous pyelogram and, if not considered dangerous, cystoscopy was undertaken. The patients were afebrile and had normal or slightly elevated sedimentation rate. Three cases of *bilateral* kidney tuberculosis should be mentioned.

The first was a woman, aged 32, with painful cystitis and several small ulcers in the bladder. The pyelogram showed bilateral changes in the upper and lower calyces. She was treated with PAS in a dose of 8 to 10 grams PAS granules a day for 14 months altogether with a few free intervals of one to two months. The pains from the cystitis improved rather soon during the treatment and after three to four months they had disappeared together with the ulcers in the bladder. After seven months there was conversion in the urine and the guinea pig test has been negative for 18 months (more than 10 examinations). The processes in the calyces have shown signs of healing—partly with calcification—on the x-ray films.

The second case was a woman of 48 years. The pyelogram showed processes in both kidneys but there was no cystitis. She was treated for 14 months without interruption with eight grams PAS granules a day (equal to 6 grams PAS). The guinea pig test was positive once during the first week of treatment. Seven consecutive tests during the following year were negative.

The third case was a man of 35 years, with complicating genital tuberculosis. In one kidney two small calcifications were seen. The urine from this kidney was positive in guinea pig innoculation. The other kidney showed an abnormal pyelogram. After eight months treatment with eight grams PAS granules a day he converted in the urine and has since been negative (14 months with eight guinea pig tests).

Two cases of *unilateral* tuberculosis have been under observation for more than one year. Both of them had kidney and genitary tuberculosis. One of the cases was not operated upon because of chronic nephritis with improper kidney function test. He was treated for six months with PAS in a dose of eight grams granules increasing to 12 grams a day without conversion in the urine. Combined therapy with chaumogra oil and streptomycin resulted in conversion within a month. The role played by PAS in this case is not easy to evaluate. Possibly the patient had converted with PAS alone as more cases did so after seven to eight months treatment.

The other case was not operated upon because the kidney process was of a type where chemotherapy alone was considered prosperous. This suggestion was verified by conversion in the urine after two months treatment with 8 to 10 grams PAS granules a day and more negative tests during six months.

Of five cases with tuberculosis in the *remaining kidney after*

nephrectomy one case had positive guinea pig test after 11 months treatment with 10 grams PAS granules a day, a hopeless case with only a minor part of the kidney intact and complicated with genital tuberculosis. His cystitis improved however and he was freed from symptoms after two to three months treatment. Another case did not convert after seven months on 8 to 12 grams PAS granules, but he is nearly free from cystitis. A third case with a minor cavity in the kidney and genitary tuberculosis converted after eight months on 8 to 10 grams PAS granules and symptoms of cystitis disappeared after two months treatment. He has remained negative for five months. The remaining two cases have been treated too short a time to be mentioned here.

Recently Linden,[17] at the annual meeting of the Swedish Surgical Association in 1948, demonstrated a case of primary renal tuberculosis which had been treated with PAS for six months prior to the nephrectomy and in which the tuberculous process was in a healing stage. Linden, therefore, considered that it would have been better in this case if nephrectomy had not been carried out. Odelberg,[18] on the same occasion, reported a case in which cystitis, pyuria and tubercle bacilli in the urine occurred six months after nephrectomy for renal tuberculosis. A tuberculous lesion was seen in the kidney (destruction of the upper calyx) and a large tuberculous ulcer of the bladder was also found. After two and one-half months treatment with PAS the patient became free from symptoms, the pyuria had disappeared and the ulcer in the bladder had healed, the change in the calyx however, remained.

Summing up the results it can be said that PAS in nearly all cases has given amelioration of the cystitis and rendered the majority free from symptoms. Ulcers in the bladder have healed. Conversion in the urine has been seen in more cases within eight months treatment and remained negative (6 to 12 months observation time). No case has shown progression on the x-ray during the treatment. A higher dosage of PAS than here used may give better results.

Skin Tuberculosis:

Lemming[10] in 1948, reported a case of chronic skin tuberculosis (history 10 years) in which healing of a hand flat sized ulcer on one foot occurred after six weeks local treatment with a 10 per cent PAS solution. This was applied with a gauze wetted in the solution and changed several times a day. There was a relapse soon after the healing but retreatment healed the ulcer again and it has remained so after-observation for more than one year.

Carstensen recently presented three cases of lupus vulgaris also treated locally with PAS with good result. One of them was treated

with Finsen light and vitamin D without success. The ulcerations around her nose prohibited her from living among other people. The disease healed on PAS within six months.

Other Forms of Tuberculosis:

Little experience has been reported on the effect of PAS on other forms of tuberculosis as othopedic and sinus tuberculosis and lymphadenitis. Orthopedic cases seem to react slowly or not at all on peroral treatment, possibly better if local treatment can be applied. Two cases of otitis have healed on peroral PAS (Smars and Kempe[19]). Cases of tuberculous peritonitis and salpingitis have also responded favorable on peoral PAS treatment.

Surgical Prophylaxis:

From a theoretical point of view PAS should be well adapted for protection in operations as resistance to PAS is not generally developed during treatment and coming late if at all. The few reports on its use pre and postoperatively are encouraging. Odelberg[20] and Bruce and co workers[21] have this year presented papers on the subject which will soon be published.

Combined Chemotherapy:

In the above presentation the use of PAS combined with other chemotherapeutics has not been mentioned. The reason for this is that representative and conclusive series have not yet been published. However, PAS combined with sulfa drugs or penicillin was early used by Vallentin in the local treatment of empyema with mixed infections and especially by Westergren and co workers[22] in pulmonary tuberculosis (peroral or parenteral). Westergren has stressed the beneficial effect of changing from one drug to another, using PAS, streptomycin, penicillin and different sulfa drugs or a few of them together. He also observed a delayed or diminished emergence of resistance to streptomycin when PAS was simultaneously given. Carstensen and co workers have, as mentioned above, used PAS continuously with shorter periods of streptomycin in miliary and encephalo-meningeal tuberculosis. Recently Kristensson[23] presented a series of far advanced and hopeless cases of pulmonary tuberculosis with multiple cavities. With combined PAS, streptomycin and penicillin given continuously all together a dramatic effect was achieved in the majority of the cases.

Ambulatory Treatment:

The absence of real toxic side effects of PAS and the peroral use invites to the ambulatory use of the drug under controlled conditions. In Stockholm Bluhm[24] has started the ambulatory

treatment in a small series from his dispensary station and presented preliminary results. In Gothenburg a similar study is going on.

When reviewing the work on PAS during the five years it has been available to use in the clinic, it must be emphasized, that the experience in many respects is rather restricted. This is partly due to the limited supplies available during the first two years and partly to the high price. Difficulties in overcoming the intestinal complaints connected to the acid character of PAS has been a third limiting factor. As the new synthesis of PAS from meta-amino-phenol simplifies the production, the supplies should be sufficient and the price acceptable. Whether PAS should be used routinely as an acid-enteric coated, or as the sodium salt, is still a question to be answered.

The optimal dose of PAS for the different forms of tuberculosis has not been satisfactory elucidated. That the highest doses (20 to 30 grams Na-PAS) should be used in cases of miliary and encephalo-meningeal tuberculosis seems justified and that lower doses than 11 to 12 grams PAS (14 grams granules) a day can be used in kidney-urinary tuberculosis due to the high concentrations in the urine. For most of the other forms of tuberculosis a dose of 10 to 12 grams PAS giving blood concentrations of two to six mg. per cent seems reasonable.

That PAS should be given *continuously,* if possible, has been illustrated by the increase in sedimentation rate and sometimes even in temperature when it has been stopped for a week or two. The length of the treatment should be determined for each case but it should be kept in mind, that even if amelioration in the general condition, the decrease in temperature and sedimentation rate are appearing early, the regressions of the lesions, at least in the lungs, are slower and the most demonstrable changes occurring between the third and sixth month. The treatment should naturally be continued as long as improvement is seen and usually the end state should be stabilized by another months treatment.

Recent investigations in vitro, in animal experiments and in the clinic seems to indicate that the combined therapy with PAS and streptomycin will give results superior to those with each drug alone. Beside that, the combined therapy has another perhaps still more remarkable feature, the depression or delay of the emergence of resistance to the drugs. This does mean that the duration of the treatment can be prolonged and perhaps widen the indication for their use.

REFERENCES

1 Lehmann, J.: The Lancet, 251:15, 1946.
2 Lehmann, J.: Svenska Lakartidningen, 43:2029, 1946.
3 Lehmann, J.: Revue Générale des Sciences, 54:222, 1947.
4 Vallentin, G.: Svenska Lakartidningen, 43:2047, 1946 and Nordisk Medicin, 33:147, 1947.
5 Vallentin, Tornell, Beskow, Carstensen, Thune, Helleberg and Lehmann, J.: Transactions of the XIV Nordiske Tuberkuloselagekongres in Copenhagen, 1948 (in press). The main part of the paper is also printed in "Le Poumon," No. 2 and 3 (March-June), p. 193, 1949.
6 Rosdhal, K. G.: Svensk Kemisk Tidskrift, 60:12, 1948 (in english).
7 Alin, K. and Helander, S.: Acta Tuberc. Scand., 22:283, 1948.
8 Alin, K. and Difs, H.: Nordisk Medicin, 33:151, 1947.
9 Dempsey, T. G. and Logg, M. H.: The Lancet, 253:871, 1947.
10 Lemming, R.: The Lancet, 256:200, 1949.
11 Lehmann, J.: Transactions of the XIV Nordiske Tuberkuloselagekongres in Copenhagen, 1948 (in press).
12 Bachman, S., Birath, G., Bruce, T., Karth, B., Lemming, R., Lindgren, G. and Lundquist, J.: Transactions of the XV Nordiske Tuberkuloselagekongres in Helsingfors, 1949 (in press).
13 Carstensen, B. and Sjolin, S.: Svenska Lakartidningen, 45:729, 1948 and "Le Poumon," No. 2 and 3 (March-June), p. 209, 1949.
14 Kallquist, I.: Transactions of the XV Nordiska Tuberkuloslakarkongress in Helsingfors, 1949 (in press).
15 Carstensen, B. and Soderhjelm, L.: Nordisk Medicin., 40:2039, 1948.
16 Ljunggren, E.: Journal D'Urologie, 1949 (in press).
17 Linden: Transaction of the Swedish Surgical Association, 1948.
18 Odelberg, A.: Ebenda.
19 Smars, G. and Kempe, S. G.: Nordisk Medicin. (in press).
20 Odelberg, A.: Paper presented at The Second Commonwealth and Empire Health and Tuberculosis Conference in London, 1949 (in press).
21 Bruce, C., Birath, G., Crafoord, C. and Uggla, L. G.: Transactions of the XV Nordiska Tuberkuloslakarkongress in Helsingfors in 1949 (in press).
22 Westergren, A.: Nordisk Medicin., 33:155, 1947.
23 Kristensson, A.: Svenska Lakartidningen, 46:1317, 1949.
24 Bluhm, I.: Transactions of the XV Nordiska Tuberkuloslakarkongress, Helsingford, 1949 (in press).

Selecting the Streptomycin Regimen for Patients with Pulmonary Tuberculosis with Special Reference to the Intermittent Dosage Schedule*

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Streptomycin research in the treatment of patients with pulmonary tuberculosis has passed through a number of stages, and in the course of these investigations, an attempt has been made to answer the following questions:

1) Is streptomycin effective in the treatment of pulmonary tuberculosis?
2) In which phase of tuberculosis is streptomycin most useful?
3) How can we overcome the toxicity factor?
4) How can we reduce the incidence of, or avoid the loss of bacterial sensitivity to streptomycin?
5) Which type of regimen should be used for the various types of cases?

Numerous investigators have substantially answered the first three questions: 1) that streptomycin is effective in the treatment of pulmonary tuberculosis, 2) that it is most effective in the treatment of recent exudative lesions, and 3) that toxicity can almost be eliminated by reduction in the dosage and length of time the drug is administered. In this preliminary report, we are attempting to summarize recent developments pertaining to the remaining two closely associated problems, namely, 4) the reduction of "bacterial resistance" to streptomycin, and 5) the type of streptomycin regimen to use.

The matter of "bacterial resistance" to streptomycin should receive first consideration, because if we render the use of this remarkable chemotherapeutic agent impossible by improper administration, we are wasting one of the most important weapons we possess in the treatment of pulmonary tuberculosis. To properly evaluate this factor, careful bacteriological studies were conducted on various streptomycin regimens at Fitzsimons General Hospital (Chart 1). It was demonstrated by this work that the shorter

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CHART 1

The Incidence of Streptomycin Resistant Tubercle Bacilli Developing During the Treatment of Pulmonary Tuberculosis by Various Dosage Schedules

(a) *Comparison of All Schedules* (SM given intramuscularly)

Regimen Number	Daily Dosage Schedules	No. of Cases (Total, 408)	Percentage Resistant* Days after Beginning of Therapy 30	60	90	120
1	2 gm, 120 days	100	0	23	46	72
2	1 gm, 120 days	37	0	18	45	67
3	1 gm, 42 days	21	0	25	25	25
4	1 gm, 28 days	67	0	8	6	5
5	½ gm, 28 days	28	0	0	0	0
6	1 gm, 28 days; repeated after 6 weeks; a total of 56 gms in 98 days	35	0	0	13	30
	Intermittent Schedules					
7	1 gm q 3 days, 120 days	50	0	2.4	17	34
8	2 gm q 3 days, 120 days	50	0	6.2	20	32
9	2 gm DHSM** q 3 days, 30 days	20	0	0	0	0

*Definition of bacterial resistance: Cultures with growth comparable to the control (0 mcg/ml) on Herrold's egg-yolk agar containing 10 mcg. of streptomycin per ml.

**Dihydrostreptomycin.

(b) *The Intermittent Schedule* (Regimens 7 and 8 above).

Therapeutic application based upon a consideration of the "resistance factor."

Days of Treatment	Per cent Resistant Cases*	*Treatment:* Use shortest course of intermittent streptomycin treatment which will accomplish results to reduce the number of cases developing "bacterial resistance."
0	0	Short courses (30-60 days) of intermittent streptomycin Rx are satisfactory for most cases of pulmonary tuberculosis with recent exudative lesions. They may be *definitive* with rest, or *adjunctive* for operations, particularly temporary collapse. Other uses include *symptomatic* treatment and as a *therapeutic trial.* NOTE LOW INCIDENCE OF RESISTANT CASES (3.9 per cent at 60 days).
30	0	
42	0	
60	3.9	
70	4.2	Long courses (60-120 days) of intermittent streptomycin treatment are better and often required in the treatment of caseous pneumonic tuberculosis (particularly acute lobular or lobar pneumonia). Its greatest usefulness in these cases is as an *adjunct* to prepare the patient for temporary collapse or surgical procedures. NOTE PROGRESSIVE INCREASE OF RESISTANCE FROM 70th TO THE 120th DAYS.
80	8	
90	18	
100	24	
110	31	
120	33	

*Studies made by the Laboratory Service, Fitzsimons General Hospital, Denver, Colorado, on one hundred (100) cases averaging three (3) cultures weekly per patient.

CHART 2

Planning Definitive Treatment for Pulmonary Tuberculosis: Based on Clinical Pathological Types.

CLASSIFICATION OF PULMONARY LESIONS: Based on progress studies—x-ray, laboratory and clinical findings. DESCRIPTIVE TERMS USED IN CLASSIFICATION APPLY TO X-RAY FINDINGS.	No.	MED RX		SURG RX	
		SM Regime	Tem Col	Per Col	Exc Sur
UNCLASSIFIED					
New patients—evaluation incomplete)	1				
NEW SOFT LESIONS					
Resolving type—good resolution (exudative)	2	Short	×		
Non-resolving—poor resolution (caseous)	3	Long	×		
Mixed (exudative and caseous)	4	Long	×		
OLD HARD LESIONS					
Cavitary (fibrocaseous cavernous)	5			×	
Localized (tuberculoma)	6	Pro			×
OLD AND NEW MIXED LESIONS					
New Component	7	S/L	×		
Old Component	8			×	×
MILIARY TUBERCULOSIS	9	Special			
APPARENTLY CURED (NTA Standards)	10				

KEY: SM—Streptomycin regimen: Short course (30-60 days; SM daily or q 3 days); Long course (60-120 days; SM daily or q 3 days); Pro—prophylactic (1 week before, 2 weeks postoperatively); S/L—Short or Long course, as indicated; Special—Special course (Long or Short courses of SM alternating with PAS).

×—Operations often required for definitive treatment.

TEM COL—Temporary collapse (pneumothorax or pneumoperitoneum).

PER COL—Permanent collapse (extra pleural thoracoplasty).

EXC SUR—Excisional surgery (segmental resection, lobectomy and pneumonectomy).

NOTE: A strict rest regime is an essential part of the management.

GENERAL PRINCIPLES OF THERAPY ILLUSTRATED IN THE CHART

(See Classification Number above)

(Great individualization is required in applying treatment and the principles summarized below are meant only to illustrate a broad viewpoint required in planning therapy. The conclusions on streptomycin are tentative, and based on current research).

1) *Unclassified:* The new patient falls in this group on admission to the hospital unless classified by previous clinical studies, serial x-ray examination or strong clinical evidence. As the clinical picture clarifies, the patient usually falls in one of the classifications below for treatment.
2) *New Soft Resolving Lesions—Good Resolution (Exudative):* Rest alone may prove to be definitive treatment. With unfavorable trend, persistent toxemia, positive sputum and/or cavitation, the plan of treatment should include streptomycin (Short regimen, 30-60 days, daily or intermittent schedules) and temporary collapse.
3) *New Soft Non-Resolving Lesions—Poor Resolution (Caseous):* As for

Number 2, except that extensive disease, particularly acute caseous pneumonia, constitutes a medical emergency and a Long course of streptomycin (60-120 days, preferably the intermittent regimen) is indicated. The fibrocaseous cavernous residuals must be treated as old hard lesions (see Numbers 5 and 6) after an appropriate period of stabilization by medical management.

4) *Mixed New Soft Resolving and Non-Resolving Lesions:* As described for Numbers 2 and 3.
5) *Old Cavitary Lesions (Fibrocaseous Cavernous):* Permanent collapse is usually required for persistent cavitary lesions, but some cases require excisional surgery when the type and location of the lesion make collapse therapy ineffective. Streptomycin is not advised except for "spreads" after thoracoplasty, or prophylactically for resection.
6) *Old Hard Localized Lesions (Tuberculoma):* Excisional surgery required. Short prophylactic course of streptomycin usually indicated (one week before, two weeks after operation).
7) *Old and New Mixed Lesions—The New Component* is usually given first attention. A short or long course of streptomycin, with or without temporary collapse, is prescribed as required.
8) *Old and New Mixed Lesions—The Old Component* may be controlled by the measures prescribed for the new lesions; if not, treatment must be surgical (see Numbers 5 or 6).
9) *Miliary:* Special long courses of streptomycin are required. This includes combinations of streptomycin and para-aminosalicylic acid (PAS) and/or alternating months of therapy with these agents.
10) *Apparently Cured (NTA Standards):* No treatment. Periodic examinations (x-ray, etc,) are required.

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the course of streptomycin and/or the smaller the daily dosage, the lower the incidence of "bacterial resistance." As compared with daily dosage schedules of similar lengths, the interrupted streptomycin schedules (streptomycin injected intramuscularly every third day) resulted in a marked delay in the emergence of resistant strains of tubercle bacilli. Other factors (cavitation, etc.) contribute to the early development of resistant strains of organisms; but when the drug is really needed, consideration of the method of administration is of paramount importance, as this factor lies within our control.

Keeping in mind the resistance studies just reviewed, consideration can now be given to other factors which influence the decision on the type of regimen to be selected for treating patients with pulmonary tuberculosis. First of all, it is of primary importance that certain principles of therapy based upon an evaluation of the pathological types of lesions be carefully reviewed before streptomycin is prescribed. Moreover, the place of this chemotherapeutic agent in the definitive treatment of pulmonary tuberculosis is largely determined by this factor, and a reasonable attempt must be made to classify the pulmonary lesions,. if treatment is to be placed on a rational basis (Chart 2). It must be determined whether or not there is a new lesion which will respond to conservative measures of therapy, or an old lesion which will require a radical approach. Every effort must be made to make this and similar decisions if treatment is to be instituted promptly, effectively and safely.

CHART 3

THE PLACE OF SM IN THE PLAN OF TREATMENT OF PULMONARY TUBERCULOSIS

The indication for the use of Streptomycin (SM) should be clearly defined at the time it is prescribed, and *there should be a real need for its use:*

I. *DEFINITIVE WITH REST TREATMENT* (Rx) (Streptomycin expected to give favorable result—arrested disease or apparent cure—without resort to other measures).
   1. New soft lesions (exudative, etc.).
   2. Some few cases of acute tuberculous pneumonia (treated early emergency).
   3. Progressive primary tuberculosis (pulmonary and glandular lesions).
   4. Miliary tuberculosis.
   5. Treatment for recent reactivation or spread in old cases.
   6. Post-hemoptoic spreads.
   7. Tuberculous complications preventing good pulmonary response to rest (bronchial, etc.).

   (Some of above may fail to respond to streptomycin and fall in other groups below).

II. *ADJUNCTIVE TO OPERATIVE PROCEDURES OF ALL TYPES:*
   1. *Preparation* for operative procedures (streptomycin used to improve operability).
      a. Lesions potentially suitable for temp coll (predom exudative, recent cavitation, etc., in which SM is used to reduce danger of complications).
         (1) To promote resolution and reduce symptoms (toxemia, sputum, etc.).
         (2) For endobronchial disease (reduce danger of tension cavities, atelectasis and/or blocked drainage).
      b. Acute and chronic caseous pneumonic cavitary tuberculosis.
         (1) If lesions are not extensive, SM may prepare for temporary collapse.
         (2) SM usually used to reduce inflammatory phase prior to permanent coll.
      c. Operable advanced bilateral disease.
         (1) Unilateral permanent collapse (worse side).
            (a) Opposite side controlled by streptomycin.
            (b) Opposite side controlled by streptomycin and temporary collapse.
         (2) Bilateral permanent collapse.
            (a) Both sides prepared by streptomycin.
      d. Inoperable cases (use of streptomycin in attempt to convert to reasonable risk for surgery).
         (1) Successful conversion.
         (2) Unsuccessful conversion (continue other Rx with or without SM).
            (a) Proceed with surgery if delay courts disaster.
            (b) Continue conventional therapy for better risk.
   2. *Prophylaxis* (Protection during and after operative procedures).
      a. Prevention of spreads during thoracoplasty for recent disease.
      b. Prevention of empyema and fistula after excisional surgery.
   3. Rx objective altered by unpredicted response to SM; combined uses of SM.
      a. "Definitive Rx" changed to "Adjunctive" if operation becomes necessary.
      b. "Adjunctive Rx" changed to "Definitive" if result warrants (unusual).
      c. "Symptomatic Rx" changed to "Adjunctive"—operation made feasible by unexpected response to streptomycin.
      d. Continuation of streptomycin for prophylaxis after use in "preparation."
   4. Other adjunctive uses.

a. Post-op reactivation or spreads (post-thoracoplasty, etc.).
b. Tuberculous complications preventing good pulmonary response (bronchial, etc.).

III. *SYMPTOMATIC TREATMENT* (Relief of distressing symptoms; no expected effect on the pulmonary lesions—far advanced "panic cases." Use cautiously!).
1. Pulmonary complications.
a. Severe painful productive cough, dyspnea, etc.
2. Non-pulmonary complications (SM may be definitive for local extrapulmonary lesions).
a. Painful ulcers of the mouth, larynx and respiratory passages.
b. Tuberculous enterocolitis with abdominal discomfort.

IV. *THERAPEUTIC TRIAL FOR PULMONARY TUBERCULOSIS SUSPECTS* (rarely necessary).
1. Serious cases, e.g., miliary suspect lacking bacteriologic proof.
2. Serious progressive lesion, tuberculosis suspect, no bacteriologic proof.

The type of regimen to select in the treatment of pulmonary tuberculosis will be almost as varied as the indications for streptomycin (Chart 3). It is important, therefore, that we clearly indicate the purpose for which streptomycin is being given, and answer certain questions relative to its use. Is it being used for 1) *definitive therapy* in which there is a reasonable chance that an apparent cure will result from the use of the drug (combined with rest therapy) without resorting to operative procedures, 2) as an *adjunct to operative procedures* in which streptomycin is prescribed with a definite feeling that it alone (combined with rest) will not bring about a favorable result, 3) for *symptomatic treatment* in which the drug is expected to relieve severe, distressing symptoms, even though the type of pulmonary disease present is such as to resist treatment, or 4) as a *therapeutic test* in which streptomycin seems indicated for urgent reasons (serious cases such as miliary tuberculosis suspects, etc.)? Viewed in this light, the benefit from streptomycin is measured not so much by its influence on the pulmonary lesion per se, but rather on its contribution to the successful management of the case. This concept is reflected in the present trend of streptomycin research, namely, that of finding the place of streptomycin in the overall plan of treatment of pulmonary tuberculosis.

It is not within the scope of this brief discussion to supply statistical tables on the clinical and x-ray results attributed to the various streptomycin regimens. In research studies made on more than 1500 patients with pulmonary tuberculosis treated with streptomycin at Fitzsimons General Hospital, the results were satisfactory when the kind and length of the treatment schedule was appropriate for the type of problem under observation (Charts 2 and 3). Aside from the long dosage schedules of one or two grams of streptomycin daily for four months, which produced

marked toxic symptoms and resistant organisms in approximately 75 per cent of the cases, there were few serious draw-backs to the regimens (Chart 1) when they were properly prescribed.

Difficulties arose in using the short courses of streptomycin therapy, because the lag in x-ray evidence of improvement (resolution) made it difficult to determine the trend of the disease in less than six to eight weeks. An attempt to overcome this handicap was made by using interrupted short courses, that is, one gram of streptomycin daily for 28 days, followed by a six weeks interval without the drug, and finally, a similar 28 day course of streptomycin for those cases in which it appeared to be indicated clinically, roentgenologically and bacteriologically. A small percentage (8 per cent) of the more active lesions (e.g., acute caseous pneumonic cavitary lesions) relapsed during the six weeks interval without chemotherapy. At the 120 day observation point, the percentage of resistant cases rose to 30 per cent. With little reduction in therapeutic efficiency, therefore, this represented a considerable decrease in the number of resistant cases as compared to the 120 day regimens of continuous daily streptomycin therapy. Furthermore, the toxic reactions to the drug as prescribed in this manner, were practically nil. This same principle of therapy was applied successfully to the intermittent streptomycin schedule, using courses of one month and rest periods of one to two months. The number of cases so treated was too small, however, for statistical analysis; but the outlook for such streptomycin regimens appears to be quite promising.

SUMMARY

On the basis of current streptomycin research studies at Fitzsimons General Hospital, certain tentative conclusions regarding the type of streptomycin regimen to select in the treatment of patients with pulmonary tuberculosis seem justified, as follows:

1) We should use the shortest course of streptomycin therapy which will accomplish our purpose, in order that we may reduce the number of cases developing "bacterial resistance."

2) That *short* courses (30-60 days) of streptomycin are satisfactory for most cases of pulmonary tuberculosis with recent exudative lesions.

3) That *long* courses (60-120 days) of streptomycin are better and often required in the treatment of patients with caseous pneumonic tuberculosis (particularly severe acute lobar or lobular pneumonia). In these cases where streptomycin may prove to be life saving, the danger of "bacterial resistance" must be disregarded.

4) That *long* courses of treatment or interrupted *short* courses

of streptomycin over a long period of time are required for miliary pulmonary tuberculosis with or without meningitis.

5) That the intermittent streptomycin schedule[1] using one or two grams of the drug every third day for one to four months, will give clinical and roentgenological results comparable to those obtained by one or two grams daily dosage schedules over similar periods of time, without significant toxic reactions to the drug. In addition, the important factor of delaying the emergence of streptomycin resistant organisms is proved. In our series, no case with "bacterial resistance" developed in 42 days; only 3.9 per cent at 60 days; 4.2 per cent at 70 days; 8 per cent at 80 days; 18 per cent at 90 days; 24 per cent at 100 days; and 33 per cent at 120 days. In other words, this effective method of using the drug can be utilized for a prolonged period with less danger of encountering "bacterial resistance" than from any of the other regimens reported upon in this study. The intermittent regimen can be used for periods of from one to four months or longer, either continuously or in interrupted short courses, depending upon the purpose for which it is prescribed. Of all courses of streptomycin therapy studied at Fitzsimons General Hospital, it appears to have the greatest utility in the management of all forms of pulmonary tuberculosis (exclusive of miliary tuberculosis), whether its purpose be for definitive treatment, as an adjunct to operative procedures, for symptomatic relief, or as a therapeutic trial. (Research studies are now being made with the intermittent streptomycin schedules combined with 12 grams of para-aminosalicylic acid (PAS) orally daily, in the hope of still further delaying the emergence of drug resistant organisms).

CONCLUSION

Selecting the type of streptomycin regimen to use in the treatment of pulmonary tuberculosis must be based upon a careful case evaluation including especially an estimation of the type of pulmonary disease present, and its potentialities to respond to therapy.

Above all else, we must consider chemotherapy as only one of the many therapeutic measures available to us, and every effort must be made to define its exact place in the plan of treatment before this drug is prescribed.

RESUMEN

Basándose en la investigación sobre estreptomicina llevada a cabo en el Hospital Fitzsimons se pueden establecer algunas con-

clusiones preliminares sobre el régimen selectivo para los enfermos de tuberculosis pulmonar:

1) Debemos usar la serie más corta de tratamiento con estreptomicina para lograr nuestro propósito a fin de disminuir el número de casos con "resistencia bacteriana."

2) Estas series *cortas* de 30 a 60 días son satisfactorias en la mayoría de los casos con lesiones exudativas recientes.

3) Las series *largas* de 60 a 120 días son mejores y a menudo requeridas en los enfermos con tuberculosis caseoneumónica (especialmente en la neumonía tuberculosa lobar aguda o lobular aguda). En estos casos cuando la estreptomicina puede ser heroica, la "resistencia bacteriana" puede no tomarse en cuenta.

4) Estas series *largas* o las *cortas* intermitentes por largo tiempo pueden ser necesarias en la tuberculosis miliar pulmonar con o sin meningitis.

5) El plan intermitente usando uno o dos gramos de droga cada tercer día por uno a cuatro meses, dará resultados clínicos y roentegenológicos comparables a los resultados obtenidos con el plan de uno a dos gramos diarios por periodos de tiempo similares sin reacciones importantes a la droga.

Además el factor importante para retardar la aparición de la estreptomicina resistencia está demostrado. En nuestras series no se encontró caso con resistencia bacteriana dentro de 42 días. Solo 3 por ciento se encontró a los 60 días; 4 por ciento a los 70 días; 8 por ciento a los 80 días; 18 por ciento a los 90 días; 24 por ciento a los 100 días y 33 por ciento a los 120 días. En otras palabras puede usarse este método efectivo de utilización de la droga por un periodo prolongado con menos peligro de encontrar "resistencia bacteriana" que en otros régimenes.

El régimen intermitente puede usarse por periodos de uno a cuatro meses o más, ya sea continuamente o en series pequeñas interrumpidas dependiendo del propósito que se tenga. De todos los métodos estudiados en el Hospital Fitzsimons parece que el más efectivo para todas las formas de tuberculosis pulmonar (excluyendo las miliares), es éste ya sea que su objeto sea como tratamiento definitivo o como adjunto del quirúrgico, como paliativo o como ensayo. (Se hacen investigaciones con la combinación de 12 gramos de Acido Para-aminosacílico, (PAS) oralmente a diario, con la esperanza de demorar la aparición de resistencia del gérmen).

CONCLUSION

La selección del régimen de estreptomicina en tuberculosis pulmonar debe basarse en la cuidadosa valuación del caso especial-

mente del tipo de enfermedad presente y sus potencialidades de respuesta al tratamiento.

Sobre todas las cosas debemos considerar la quimioterapia como uno de los muchos recursos disponibles y todo esfuerzo debe hacerse para definir su lugar exacto en el plan antes de que la droga se prescriba.

REFERENCE

1 Deyke, V. F., et al: "Intermittent Dosage Schedules of Streptomycin with Resultant Prolonged Sensitivity in M. Tuberculosis," *Ann. Int. Med.*, 30:619, 1949. (Preliminary Report from Fitzsimons Gen. Hosp.).

Factors Influencing the Outcome of Streptomycin Therapy of Pulmonary Tuberculosis*

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Increasingly representative data are becoming available on many phases of the effects of streptomycin therapy in tuberculosis. The American Trudeau Society has recently published the report of its cooperative investigation in pulmonary tuberculosis,[1,2] and the United States Public Health Service is presently in the process of compiling the results of its streptomycin study. The cooperative investigation of the Veterans Administration, Army and Navy has prepared four reports of its experience for publication,[3-6] in addition to interim reports and distribution of the *Minutes* of its semi-annual Streptomycin Conferences, of which eight have been held.

The largest of these studies, that of the Veterans Administration, Army and Navy, has permitted a limited analysis of certain variables, such as variations in streptomycin regimen, in a body of clinical data of considerable uniformity. In a summary of its experience from July 1946, to April 1949, totalling 4500 cases of tuberculosis, including 2000 cases of pulmonary tuberculosis, this study has indicated the following:[6,7]

1. Reducing the daily dosage of streptomycin from 2 grams to 1 gram to 0.5 gram has successively reduced the incidence of all important toxic manifestations; reducing the duration of administration of the drug from 120 days to 60 days to 42 days likewise is associated with reduced toxicity. A reduction of the number of injections into which the total daily dosage is divided has also been associated with decreased incidence of toxicity. These observations apply particularly to vestibular dysfunction, impairment of renal function, dermatitis, and such other manifestations as may be sufficiently severe to compel cessation of streptomycin therapy.

2. Strains of tubercle bacilli resistant to 10 mcgm. per ml. or more of streptomycin emerge at a fairly regular rate, which appears to be independent of daily dosage in the ranges studied, but definitely related to duration of therapy. At the end of 42 days of daily administration approximately 35 per cent of specimens examined are resistant to 10 mcgm. per ml. or more; at the end of 60 days, 50 per cent; at the end of 120 days, 75 per cent. Administration of streptomycin alone every third day, or

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combining daily administration with para-aminosalicylic acid (PAS), materially reduces these rates.

3. Different tuberculous conditions respond at different rates to streptomycin therapy, and some individualization of therapy appears to be indicated according to the condition to be treated. Whereas data for extra-pulmonary tuberculous conditions are not as complete as for pulmonary tuberculosis, it appears that the relative effect of different streptomycin regimens is much the same for extra-pulmonary tuberculosis as for pulmonary tuberculosis.

4. Considerable uniformity of therapeutic results has been observed in the treatment of approximately 2000 cases of pulmonary tuberculosis on seven different streptomycin regimens, particularly with respect to rates of x-ray improvement, relapse, sputum conversion, and mortality, as well as such clinical signs as reduction of fever, decrease in sputum volume, and weight gain.

5. However, critical statistical analysis reveals certain differences in x-ray response to treatment in essentially homogeneous groups of cases of pulmonary tuberculosis, with slightly but significantly superior results from regimens of higher daily dosage and greater duration.

6. The therapeutic superiority of such regimens, on the other hand, is tempered by the markedly greater toxicity of the larger daily dosages (2 gms./day), and the definitely higher rate of emergence of streptomycin-resistant tubercle bacilli of the regimens of longer duration (120 days).

7. For this reason it is concluded that, whereas the "best" streptomycin regimen has not yet been determined, one gram a day appears to be a satisfactory daily dosage, and that duration of therapy should generally not exceed 42 or 60 days, until procedures designed for delaying the emergence of streptomycin-resistant strains of tubercle bacilli have been adequately standardized.

In the analysis referred to in paragraph five above, of the x-ray changes in cases of pulmonary tuberculosis treated on different streptomycin regimens[6,7] the important data are as given in Table I.

From these data it is observed that, on the 120-day regimens, there is no significant difference in the incidence of *all* degrees of x-ray improvement; nor any significant difference on regimens of 2 grams a day for 120 and 60 days. Differences in all x-ray improvement are significant for 1 gm. and 0.5 gm. regimens between 120 and 42 day durations, and between the two 42 day regimens. If, in addition to observing the fact of any degree of improvement by x-ray observation, the *degree* of improvement is also taken into account, and the incidence of *"moderate and marked"* improvement is compared among regimens (Part B of Table I), differences of statistical significance are more numerous, and are not present only between the following regimens: 2 grams a day for 120 days and 1 gram a day for 120 days; and 0.5 gram a day for 120 days and 1 gram q. three days for 120 days.

The data collected by the Veterans Administration, Army and Navy have been derived from "summary reports" submitted by

the cooperating study units according to Tables outlined in advance of each semi-annual Streptomycin Conference. Such summary reports have in general permitted little or no cross-tabulation of variables other than those of regimens. For the Seventh Conference, in April 1949, however, some cross-tabulations were possible.[7] Individual case reports are now being assembled to permit an extension of statistical analysis beyond that hitherto possible in this study.

Table II presents cross-tabulations with respect to x-ray changes, from data gathered for the Seventh Streptomycin Conference for cases of pulmonary tuberculosis treated with streptomycin for 42 days (1 gram a day and 0.5 gram a day for 42 consecutive days, and 1 gram every third day for 120 days). Similar cross-tabulations are not available for regimens which the study employed prior to April 1948, (2, 1, and 0.5 grams daily for 120 days, and 2 grams daily for 60 days).

From Table II it is seen that cavernous cases of pulmonary tuberculosis improve more frequently by x-ray observation, 120 days after the start of therapy, when homolateral collapse is employed than when it is not, with respect to all degrees of x-ray improvement (74 per cent and 61 per cent respectively), and to marked x-ray improvement (22 per cent and 13 per cent respectively). According to the pre-streptomycin course of the disease

TABLE I.

COMPARISON OF X-RAY IMPROVEMENT 120 DAYS AFTER START OF STREPTOMYCIN THERAPY

A. All Degrees of X-Ray Improvement

Daily Dose (gms.)	Duration of Treatment (days)	No. of Cases	Per Cent Improved		Per Cent Improved	No. of Cases	Duration of Treatment (days)
2	120	372	82	—	79	78	60
1	120	398	80	*	70	647	42
0.5	120	121	80	*	60	259	42
1 q. 3 d.	120	82	76		—	—	—

B. Marked and Moderate X-ray Improvement

2.	120	372	66	*	52	78	60
1	120	398	64	*	47	647	42
0.5	120	121	57	*	41	259	42
1 q. 3 d.	120	82	49		—	—	—

In two center columns (per cent improved), chi-square test has been applied to adjacent pairs: * signifies difference is statistically significant, — signifies difference is not satistically significant.

(judged by a comparison of films in the two to three months immediately preceding the start of therapy), regressive disease improves most frequently (80 per cent all improvement, 21 per cent marked improvement), progressive disease almost as frequently (70 per cent all improvement, 20 per cent marked improvement), and stationary disease least (65 per cent all improvement, 13 per cent marked improvement). The difference in response according to predominance of exudation, whether judged to be over or under 50 per cent, is insignificant with respect to all x-ray improvement (68 per cent and 69 per cent), but those cases judged to be predominantly exudative (51 per cent to 100 per cent exudative) have more marked x-ray improvement at 120 days than those judged to be 0 to 50 per cent exudative (21 per cent and 14 per cent, respectively). According to stage of the disease at the start of treatment, moderately advanced cases improve more (82 per cent all x-ray improvement, 30 per cent marked x-ray improvement), and far-advanced cases less (65 per cent all x-ray improvement, 15 per cent marked x-ray improvement). Too few cases of minimal disease (9) are available for comment.

Table III presents similar cross-tabulations for data from the same source (on 42 day treatment cases) with respect to the relationship of certain variables to sputum conversion, both on direct smear and by culture (negative for at least three months in each instance).

There are few surprises in this table: sputum conversion in all categories is slightly lower percentagewise by culture than by direct smear; conversion is more frequent with collapse than without, although the difference perhaps is not as striking as might have been anticipated; and far-advanced disease has the lowest sputum conversion rates. Comparably analytic data are not available for sputum conversion more than 120 days after the start of treatment.

In Tables II and III questions arise which suggest the relative analytic incompleteness of the data presented. Are cases receiving the benefit of collapse therapy comparable to those not receiving it? What kind of collapse therapy was employed, and when, in relation to the results noted? Is extent of the disease aside from the characteristics listed important? Many other questions will occur to the inquiring physician and scientist, the answers to which would make possible more precise indications for streptomycin therapy, and its employment in conjunction with other standard forms of therapy such as bed rest, collapse therapy, etc. Amberson, in commenting on the data of the Veterans Administration, Army and Navy, has pointed to some areas where more information is needed:[9]

TABLE II.

EFFECT OF VARIABLES ON X-RAY CHANGE IN CASES OF PULMONARY TUBERCULOSIS TREATED WITH STREPTOMYCIN FOR 42 DAYS

(Cross-Tabulations from Table I, Parts C, D, E, F, Minutes of the Seventh Streptomycin Conference, Denver, April 21-24, 1949)

	X-ray Change 120 Days After Start of Treatment											
	Marked Impr.		Slt.-Mod. Impr.		All Impr.		No Change		Worsening		TOTAL CASES	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
A. EFFECT OF HOMOLATERAL COLLAPSE												
1. Cavitary Component Absent/Unknown (with and without collapse)	42	22	98	52	140	74	25	13	24	13	189	19
2. With homolat. collapse	83	22	189	52	272	74	32	9	61	17	365	36
3. Without homolat. collapse	60	13	218	48	278	61	73	16	106	23	457	45
Totals	185	18	505	50	690	68	130	13	191	19	1011	100
B. EFFECT OF PRE-STREPTOMYCIN COURSE OF DISEASE												
1. Trend Unknown	3	11	9	35	12	46	3	12	11	42	26	3
2. Disease Regressive	6	21	17	59	23	80	3	10	3	10	29	3
3. Disease Stationary	29	13	109	52	138	65	51	24	23	11	212	21
4. Disease Progressive	146	20	366	50	512	70	71	9	153	21	736	73
Totals	184	18	501	50	685	68	128	13	190	19	1003	100
C. EFFECT OF PREDOMINANCE OF EXUDATION												
1. Extent Unknown	3	20	5	33	8	53	4	27	3	20	15	2
2. 0-50% Exudative	51	14	196	54	247	68	66	18	50	14	363	36
3. 51-100% Exudative	130	21	300	48	430	69	58	9	137	22	625	62
Totals	184	18	501	50	685	68	128	13	190	19	1003	100
D. EFFECT OF STAGE OF DISEASE												
1. Stage Unknown	0	0	1	20	1	20	1	20	3	60	5	*
2. Minimal	0	0	5	56	5	56	2	22	2	22	9	1
3. Moderately Advanced	67	30	114	52	181	82	19	9	21	9	221	22
4. Far Advanced	117	15	381	50	498	65	106	14	164	21	768	77
Totals	184	18	501	50	685	68	128	13	190	19	1003	100

*—less than 0.5 per cent.

"It is felt that the figures relating to cavitary component add very little information, largely because they do not afford any data relative to the recency, chronicity, activity, or morphology of the cavity . . . ."; again, "It would be desirable to know more about the response (of exudative lesions) in relation to the duration and acuteness of pneumonic lesions . . . ."; and again, "The geographic extent of the disease had no apparent effect on the development of drug resistance, and generally speaking it is thought that the character of a lesion is more important than its extent."

To such questions as these, and to many others, numerous independent investigators are applying themselves. In the belief that careful analysis of smaller bodies of clinical data than those cited, uniformly observed, may point the way to answers to some of

TABLE III

EFFECT OF VARIABLES ON SPUTUM CONVERSION IN CASES OF PULMONARY TUBERCULOSIS TREATED WITH STREPTOMYCIN FOR 42 DAYS

(Cross-Tabulations from Table I, Minutes of the Seventh Streptomycin Conference)

	Sputum Conversion 120 Days After Start SM					
	BY DIRECT SMEAR			BY CULTURE		
	No. of Determinations	Converted No.	Converted Pct.	No. of Determinations	Converted No.	Converted Pct.
A. EFFECT OF HOMOLATERAL COLLAPSE						
Cavernous Cases Only						
With homolateral collapse	411	133	32	345	87	25
Without homolateral collapse	484	110	23	415	76	18
Sub-Total, cavernous	895	243	27	760	163	21
Cavitary component absent or unknown (with and without homolateral collapse)	180	88	49	159	72	46
Totals	1075	331	31	919	235	26
B. EFFECT OF COLLAPSE ACCORDING TO STAGE OF DISEASE (Irrespective of Cavities)						
With Collapse						
Minimal	1	1	100	1	1	100
Moderately Advanced	98	51	52	93	38	41
Far Advanced	378	117	31	309	74	24
Sub-Tot. with collapse	477	169	35	403	113	28
Without Collapse						
Minimal	7	6	86	5	4	80
Moderately Advanced	121	73	60	111	55	50
Far Advanced	460	80	17	393	62	16
Sub-Tot. without collapse	588	159	27	509	121	24
With/Without Collapse						
Minimal	8	7	88	6	5	83
Moderately Advanced	219	124	57	204	93	46
Far Advanced	838	197	24	702	136	19
Totals	1065	328	31	912	234	26

these questions, the experience of the Tuberculosis Service of the Minneapolis Veterans Administration Hospital in the streptomycin treatment of pulmonary tuberculosis has been reviewed, and the balance of this presentation will be concerned chiefly with its results.

Methods and Materials

The Minneapolis Streptomycin Study Unit has been a part of the cooperative investigation of the Veterans Administration, Army and Navy since January 1947. Its cases of pulmonary tuberculosis have been selected according to the protocol agreed upon by the cooperating investigators, which provides essentially that cases shall be progressive or at best stationary, and that x-rays shall disclose some exudative component, the more the better. Recent disease is preferred. Minimal disease is usually considered inappropriate for treatment. Activity of the patient is limited to that in effect prior to streptomycin therapy and is maintained at this level during treatment and for four months thereafter. With treatment regimens of different durations, the four-month period immediately following the start of therapy has been arbitrarily adopted as the "treatment period," and follow-up periods of six months each, following this treatment period, have been the standard units of observation in time.

The Minneapolis Study Unit treated its first cases with 2 grams of streptomycin a day for 120 days, beginning in February 1947, and later in that year cases were treated with 2 grams a day for 60 days and then 1 gram a day for 120 days. Observation is possible for 22 months from the start of treatment (the four-month treatment period and three six-month follow-up periods) in 32 such cases, designated as having been treated on "old" regimens. Alternation of treatment on regimens of 1.0 gram and 0.5 gram a day for 42 days was begun in April 1948, and on such "new" regimens observation is available on 25 cases for 10 months (the four-month treatment period and one six-month follow-up period).

These 57 cases, designated as "protocol cases," constitute the principal body of clinical material to be analyzed. Recognizing, however, that the restrictions of the protocol necessarily limit the variety of disease subjected to streptomycin therapy, the Minneapolis Study Unit has analyzed an additional 29 cases, designated as "non-protocol cases" in a manner similar to that applied to the protocol cases.[10] These non-protocol cases are those which had active pulmonary tuberculosis at the time they received streptomycin therapy primarily for extra-pulmonary tuberculosis. In the analysis to follow these 29 cases will generally be considered separately from the protocol cases.

As already intimated, it is believed to be of the utmost importance that classification of cases of pulmonary tuberculosis be as meaningful and complete as possible, particularly with respect to the degree of acuteness of the inflammatory tuberculous process. Designation of stage of the disease, cavitary component, and the pre-streptomycin course do not fully describe tuberculous pulmonary lesions, although "predominance of exudation" is helpful in a rough way.

Desiring to avoid the semantic problem of such terms as exudative, productive, and fibrotic, and agreeing with Medlar[11] that "no one phase (of the tuberculous process) is completely independent of its predecessor and . . . all tuberculous lesions do not necessarily undergo the same evolution," the Minneapolis Study Unit adopted a "pathologic" scale of acuteness, consisting of three degrees each of acute, subacute, and chronic inflammatory tuberculous disease, which it has found helpful and meaningful in its

TABLE IV

AGREEMENT AMONG "JURORS"

As to Classification of Activity of Inflammatory Process in 26 Cases of Pulmonary Tuberculosis from "0-Day" X-ray Only (on 9-point scale)

Points Deviation from Mean	Dr. No. 1	Dr. No. 2	Dr. No. 3	Dr. No. 4	Dr. No. 5	Total	Pct.	Tot.
RELATIVELY MIXED								
0	17	11	4	9	10	51	53)	
1	4	7	8	8	9	36	37)	90
2		2	1	4	2	9	9	
3		1				1	1	
Total Ratings	21	21	13	21	21	97	100	
Total Deviation	4	14	10	16	13	57		
Avge. Deviation	0.19	0.67	0.77	0.76	0.62	0.59		
MIXED								
0	9	3		2	1	15	54)	
1	1	2	1	2	4	10	38)	92
2					1	1	8	
Total Ratings	10	5	1	4	6	26	100	
Total Deviation	1	2	1	2	6	12		
Avge. Deviation	0.1	0.4	1.0	0.5	1.0	0.46		
ALL CASES								
0	26	14	4	11	11	66	54)	
1	5	9	9	10	13	46	37)	91
2		2	1	4	3	10	8	
3		1				1	1	
Total Ratings	31	26	14	25	27	123	100	
Total Deviation	5	16	11	18	19	69		
Avge. Deviation	0.16	0.62	0.79	0.72	0.70	0.56		

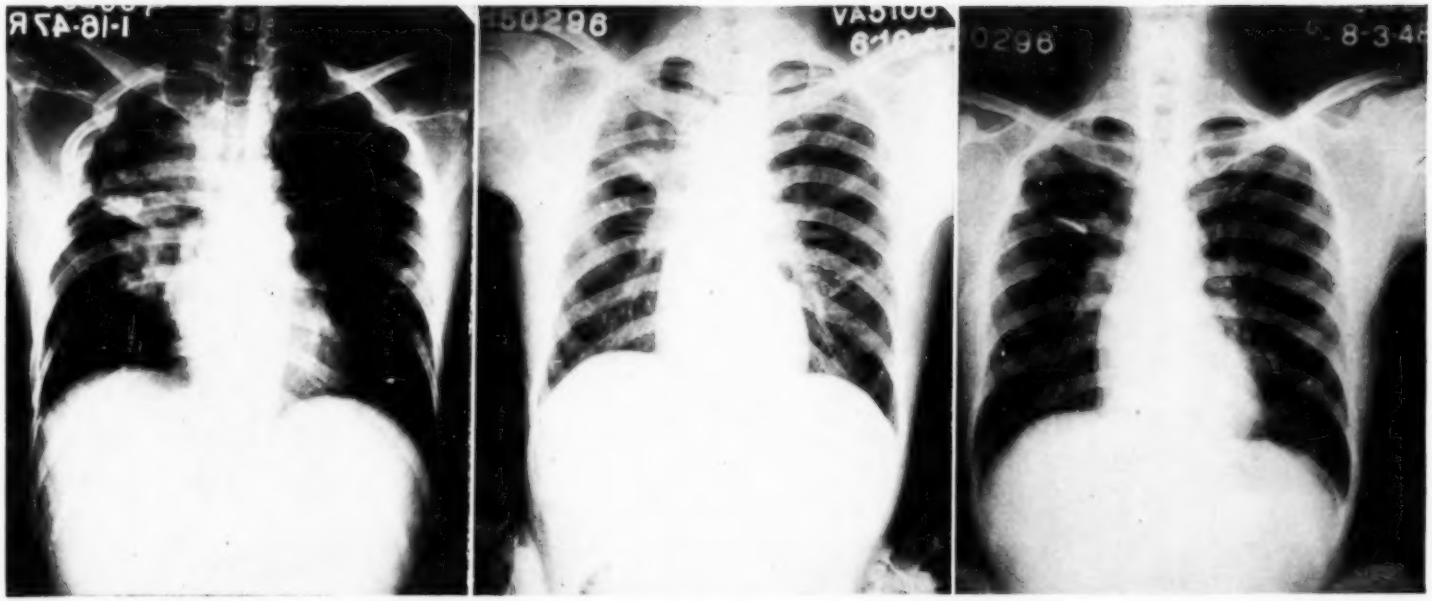

FIGURE 1a FIGURE 1b FIGURE 1c

Fig. 2: (J.A.) Young World War II White veteran, pulmonary tuberculosis and tuberculous laryngitis.—*Fig. 2a:* April 2, 1947: disease classed as "unmixed" subacute (almost chronic) (see text).—*Fig. 2b:* June 30, 1947: start of treatment with streptomycin (2 gms./day for 120 days), no change in pre-streptomycin period.—*Fig. 2c:* September 22, 1948: moderate x-ray improvement about 15 months after start of therapy. Sputum negative by culture for approximately one year. No relapse since.

evaluation of the results of streptomycin therapy. A most important part of such a classification is the recognition that nearly all cases fall quite easily into "relatively unmixed" stages of acuteness of the inflammatory tuberculous process, or into "mixed" categories, combining nearly always a definitely chronic component with either an acute or a subacute inflammatory component. In the former as far as can be determined clinically there is relatively little admixture of more than one of the three stages; in the latter a clear mixture of more than one. In this analysis "unmixed" *chronic* cases from the "non-protocol" group have been omitted, and all "unmixed" cases, either protocol or non-protocol have been classified as acute or subacute. A previous report[10] has indicated that "unmixed" subacute "non-protocol" cases appear to respond to streptomycin therapy in a manner almost identical with "unmixed" acute "protocol" cases. Figure 1a illustrates a case of unmixed acute disease, Figure 2a a case of unmixed subacute disease, and Figure 3a a case of mixed disease (combining chronic with acute).

The validity of such a scale of acuteness of the inflammatory tuberculous process has been tested by submitting 26 cases to a "panel" of five physician "jurors," who, without prior experience in such a classification, were asked to rate each case from a single x-ray, without clinical or other data, on a nine-point scale. Table IV summarizes the degree of agreement encountered in this unrehearsed test. It will be seen (bottom line of Table IV) that the average departure from the mean rating of the "jurors" for each case was 0.56 point on the nine-point scale. In only one instance was there a departure from the mean of three points, and in 91 per cent of the ratings there was either perfect agreement with or not more than a one-point departure from the mean. Such a test is not intended to demonstrate accuracy of correlation between x-ray findings and pathology, but does demonstrate, it is believed, that ratings of acuteness of the inflammatory tuberculous process can be made from x-rays by experienced physicians with reliability and validity.

The investigation of the Veterans Administration, Army and Navy has adopted a scale of x-ray change which may be applied to a comparison of any two x-rays of a given patient:

1 — marked improvement
2 — moderate improvement
3 — slight improvement
4 — no change
5 — slight worsening
6 — moderate worsening
7 — marked worsening

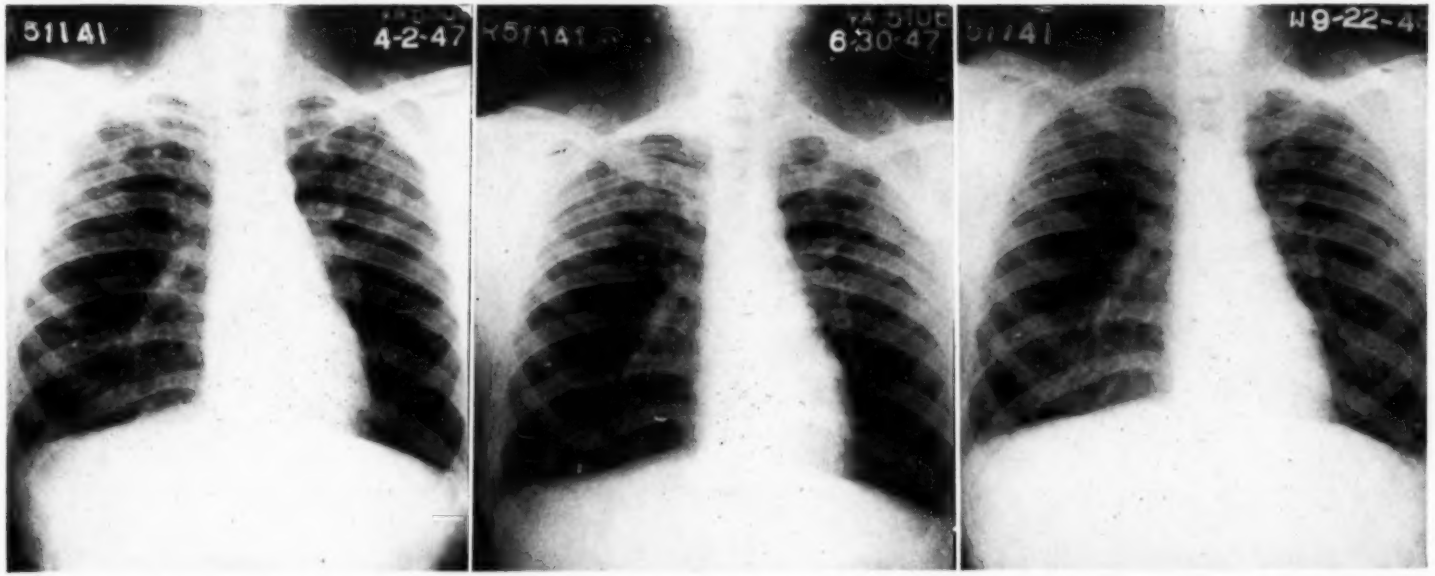

FIGURE 2a FIGURE 2b FIGURE 2c

Fig. 2: (J.A.) Young World War II White veteran, pulmonary tuberculosis and tuberculous laryngitis.—*Fig. 2a:* April 2, 1947: disease classed as "unmixed" subacute (almost chronic) (see text).—*Fig. 2b:* June 30, 1947: start of treatment with streptomycin (2 gms./day for 120 days), no change in pre-streptomycin period.—*Fig. 2c:* September 22, 1948: moderate x-ray improvement about 15 months after start of therapy. Sputum negative by culture for approximately one year. No relapse since.

This scale has been employed by the Minneapolis Study Unit, with the slight modification of adding two extremes: those of "very marked improvement," and "very marked worsening" (nearly always leading to death). Every effort has been made to make each point on the scale on either side of "no change" uniform in depth or breadth. For the purposes of this report the first two points on the Minneapolis scale have been grouped together to constitute "marked improvement."

Figures 1 to 3, in addition to illustrating the major classifications of the scale of acuteness of the inflammatory tuberculous process, also illustrate the degrees of improvement by x-ray observation employed in analysis of data. In each Figure three x-rays are shown: (a) at the start of treatment, (b) at the end of the 4-month treatment period, and (c) a follow-up x-ray. By comparing films (a) and (b) the change in the treatment period may be determined; by comparing films (a) and (c) total change from start of treatment may be rated.

The ratings of change in these three cases which have been made by the Minneapolis Study Unit have been as follows:

Fig. No.	"Acuteness"	Change at 4 months	Follow-up Change
1	Acute	Marked improvement	Very marked improvement
2	Subacute	Slight improvement	Moderate improvement
3	"Mixed" (chronic & acute)	Slight improvement	Slight to moderate improvement

Results

Table V gives the results of the analysis of 86 cases of pulmonary tuberculosis according to the characteristics and observations described. On the horizontal axis of Part A of this Table are given the defining characteristics of each group, in accordance with the practice of the larger streptomycin study of the Veterans Administration, Army and Navy. On the horizontal axis of Part B of this Table are given the results of treatment in each group: x-ray improvement (both of all degrees and "marked" improvement), at four months, 10 months, and 22 months after the start of therapy; the incidence of relapse by x-ray observation at the latter two points in time; the extent to which collapse therapy has been employed in the same periods; sputum conversion, either at 10 months or 22 months after the start of therapy; and the cumulative mortality to date.

On the vertical axis of Table V, in both Parts A and B, are listed the 16 groups into which the 86 cases have been divided, according to whether each case is:

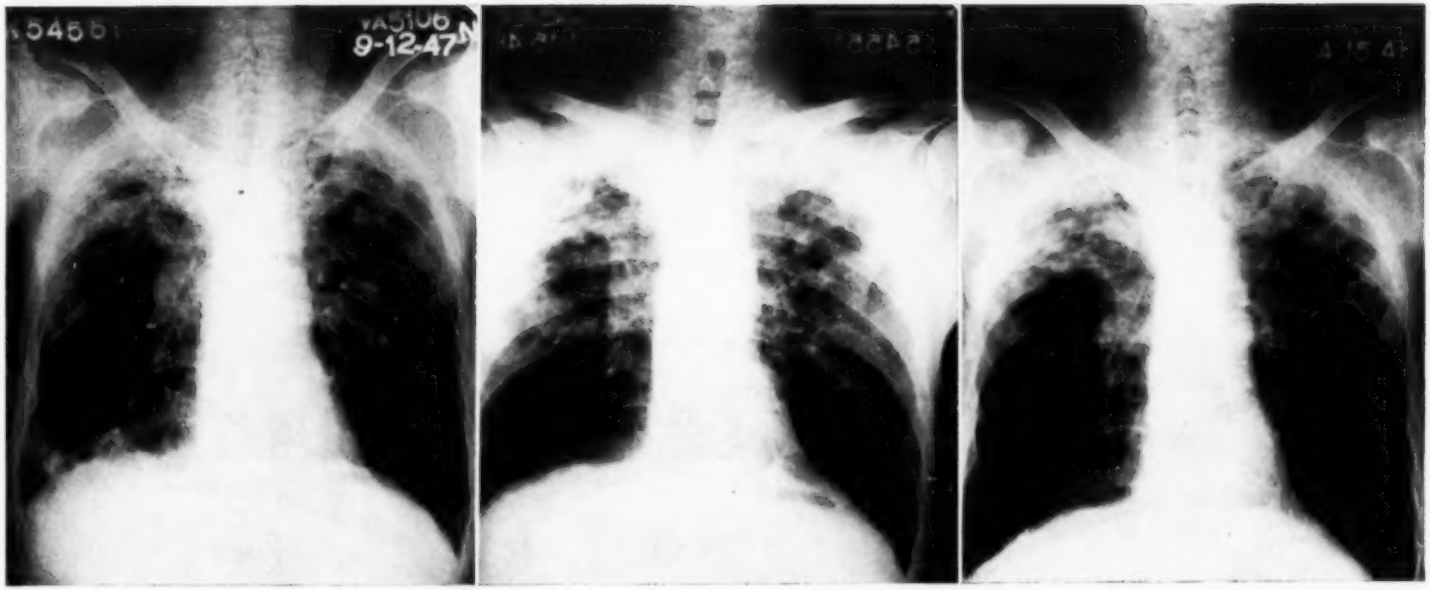

FIGURE 3a FIGURE 3b FIGURE 3c

Fig. 3: (J.P.) 55-year-old World War I White veteran, pulmonary tuberculosis, and tuberculosis of tongue.—*Fig. 3a:* September 12, 1947: approximately stationary disease except for recent spread into right base, classed as "mixed" chronic and acute (see text), just after start of streptomycin therapy.—*Fig. 3b:* January 15, 1948: very slight improvement at end of streptomycin therapy (2 gms./day for 120 days), and tuberculous ulcer of tongue healed.—*Fig. 3c:* April 15, 1948: slight to moderate improvement seven months after start of therapy. Transferred to another hospital, patient has subsequently had a slight relapse, sputum remains positive, but he is still living.

"protocol" or "non-protocol"
treated on an "old" or a "new" regimen
treated or not treated with collapse therapy
predominantly "unmixed" or "mixed" with respect to the acuteness of inflammatory disease.

Except for differences in duration of observation after initiation of streptomycin therapy, cases treated on "old" and "new" regimens have been found to be quite comparable, and have been grouped together in lines 17 to 24 of this Table, thus eliminating the variable of regimen. This is in accordance with the finding in the larger study that differences in results according to regimen are relatively slight and less significant than according to other variables, and to the observation of the Minneapolis Study Unit that "It is not felt that any differences . . . . between groups . . . . are related to dosage and duration of streptomycin therapy."[10]

In lines 25 to 28 on the vertical axis of Table V regrouping eliminates the variable of collapse therapy, and lines 29 and 30 give the totals for "protocol" and "non-protocol" cases separately. Line 31 gives the total experience for the entire 86 cases. Groupings from this table other than those indicated are readily available to the interested analyst.

Protocol Cases

From Table V-A it will be seen that there is relatively little difference in defining characteristics tabulated for the 35 "unmixed" cases (Group 25) and 22 "mixed" cases (Group 26), with the following differences being the most important: the "mixed" cases are slightly more far-advanced, and have cavities demonstrable more frequently.

There is a considerable difference between these two groups in clinical results, as is seen in Table V-B. Whereas the "unmixed" cases, with respect to all degrees of x-ray improvement (columns 11, 13, and 16), were 100 per cent improved at four months, 94 per cent at 10 months, and 82 per cent (14 of 17 cases, Groups 1 and 3) at 22 months after the start of treatment, the corresponding figures for the "mixed" group were: 73 per cent at four months, 50 per cent at 10 months, and 40 per cent (six of 15 cases, Groups 5 and 7) at 22 months. The figures for the "unmixed" group with respect to marked x-ray improvement (columns 12, 14 and 17) are: 26 per cent at four months, 77 per cent at 10 months, and 82 per cent at 22 months. The "mixed" group show marked x-ray improvement in 0 per cent at four months, in 32 per cent at 10 months, and in 33 per cent at 22 months. There is a corresponding disparity for the relapse rates (columns 15 and 18) at both 10 and 22 months after the start of streptomycin therapy for these two

TABLE V. A.

CHARACTERISTICS DEFINING GROUPS
IMMEDIATELY PRIOR TO START OF STREPTOMYCIN THERAPY

Group No.	Treatment Groups	Group Designation*	Number of Cases in Grp.	Stage of Disease M.A. Min.	Stage of Disease M.A. F.A.	Pre-SM Course Regressive	Pre-SM Course Stationary	Pre-SM Course Progressive	Cavities Demonstrable	Cavities Not demonstrable	Predominance of Exudation 51-100 Pct.	Predominance of Exudation 0-50 Pct.
	(Column No.)			(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
	CASES TREATED ON VA SM PROTOCOL											
	Disease Relatively "Unmixed"**											
	With Collapse Therapy											
1.	"Old" Regimens**, 22 mo. F-U	IA1a	11	0	0	11	1	2	8	8	3	10	1
2.	"New" Regimens**, 10 mo. F-U	IB1a	11	0	2	9	1	1	9	11	0	9	2
	Without Collapse Therapy												
3.	"Old" Regimens, 22 mo. F-U	IA1b	6	0	0	6	0	3	3	2	4	4	2
4.	"New" Regimens, 10 mo. F-U	IB1b	7	0	4	3	0	1	6	4	3	5	2
	Disease "Mixed"** (Acute & Chronic)												
	With Collapse Therapy												
5.	"Old" Regimens, 22 mo. F-U	IA2a	1	0	0	1	0	1	0	0	1	1	0
6.	"New" Regimens, 10 mo. F-U	IB2a	2	0	1	1	0	2	0	2	0	2	0
	Without Collapse Therapy												
7.	"Old" Regimens, 22 mo. F-U	IA2b	14	0	0	14	1	3	10	11	3	11	3
8.	"New" Regimens, 10 mo. F-U	IB2b	5	0	0	5	0	0	5	5	0	3	2
	NON-PROTOCOL CASES**												
	Disease Relatively "Unmixed"**												
	With Collapse Therapy												
9.	"Old" Regimens, 22 mo. F-U	IIA1a	7	1	1	5	0	7	0	5	2	1	6
10.	"New" Regimens, 10 mo. F-U	IIB1a	1	0	1	0	1	0	0	1	0	0	1
	Without Collapse Therapy												
11.	"Old" Regimens, 22 mo. F-U	IIA1b	8	1	6	1	1	5	2	1	7	1	7
12.	"New" Regimens, 10 mo. F-U	IIB1b	4	0	3	1	0	4	0	1	3	1	3
	Disease "Mixed"** (Acute & Chronic)												
	With Collapse Therapy												
13.	"Old" Regimens, 22 mo. F-U	IIA2a	2	0	0	2	0	1	1	2	0	1	1
14.	"New" Regimens, 10 mo. F-U	IIB2a	0	0	0	0	0	0	0	0	0	0	0
	Without Collapse Therapy												
15.	"Old" Regimens, 22 mo. F-U	IIA2b	6	0	0	6	0	3	3	6	0	2	4
16.	"New" Regimens, 10 mo. F-U	IIB2b	1	0	0	1	0	0	1	1	0	1	0

16. New Regimens, 10 mo. F-U	IIB2b	1	0	0	1	0	0	1	1	0	1	0
SUB-TOTALS												
PROTOCOL CASES												
Disease Relatively "Unmixed"												
17. With Collapse Therapy	I1a	22	0	2	20	2	3	17	19	3	19	3
18. Without Collapse Therapy	I1b	13	0	4	9	0	4	9	6	7	9	4
Disease "Mixed" (Acute & Chronic)												
19. With Collapse Therapy	I2a	3	0	1	2	0	3	0	2	1	3	0
20. Without Collapse Therapy	I2b	19	0	0	19	1	3	15	16	3	14	5
NON-PROTOCOL CASES												
Disease Relatively "Unmixed"												
21. With Collapse Therapy	II1a	8	1	2	5	1	7	0	6	2	1	7
22. Without Collapse Therapy	II1b	12	1	9	2	1	9	2	2	10	2	10
Disease "Mixed" (Acute & Chronic)												
23. With Collapse Therapy	II2a	2	0	0	2	0	1	1	2	0	1	1
24. Without Collapse Therapy	II2b	7	0	0	7	0	3	4	7	0	3	4
PROTOCOL CASES												
25. Disease "Unmixed" (lines 17, 18)	I1	35	0	6	29	2	7	26	25	10	28	7
(Per cent of Group 25)		(100)	(0)	(17)	(83)	(6)	(20)	(74)	(71)	(29)	(80)	(20)
26. Disease "Mixed" (lines 19, 20)	I2	22	0	1	21	1	6	15	18	4	17	5
(Per cent of Group 26)		(100)	(0)	(5)	(95)	(5)	(27)	(68)	(82)	(18)	(77)	(23)
NON-PROTOCOL CASES												
27. Disease "Unmixed" (lines 21, 22)	II1	20	2	11	7	2	16	2	8	12	3	17
(Per cent of Group 27)		(100)	(10)	(55)	(35)	(10)	(80)	(10)	(40)	(60)	(15)	(85)
28. Disease "Mixed" (lines 23, 24)	II2	9	0	0	9	0	4	5	9	0	4	5
(Per cent of Group 28)		(100)	(0)	(0)	(100)	(0)	(44)	(56)	(100)	(0)	(44)	(56)
TOTALS												
29. ALL PROTOCOL CASES (lines 25, 26)	I	57	0	7	50	3	13	41	43	14	45	12
(Per cent of Group 29)		(100)	(0)	(12)	(88)	(5)	(23)	(72)	(75)	(25)	(79)	(21)
30. NON-PROTOCOL CASES (lines 27, 28)	II	29	2	11	16	2	20	7	17	12	7	22
(Per cent of Group 30)		(100)	(7)	(38)	(55)	(7)	(69)	(24)	(59)	(41)	(24)	(76)
31. GRAND TOTAL—ALL CASES		86	2	18	66	5	33	48	60	26	52	34
(Per cent of Total)		(100)	(2)	(21)	(77)	(6)	(38)	(56)	(70)	(30)	(60)	(40)

*—Group designation symbols as follows:
I—Protocol Cases A—"Old" Regimens** 1—"Unmixed" Disease** a—with collapse therapy
II—Non-Protocol Cases B—"New" Regimens** 2—"Mixed" Disease** b—without collapse therapy
**—see text for definition and explanation
Abbreviations: SM = streptomycin; F-U = follow-up (from start of treatment);
Min. = minimal; M.A. = moderately advanced; F.A. = far advanced.

TABLE V. B.

RESULTS OF STREPTOMYCIN TREATMENT—INCIDENCE OF IMPROVEMENT AND RELAPSE BY X-RAY OBSERVATION AFTER START OF STREPTOMYCIN TREATMENT

Group No.	TREATMENT GROUPS	Group Designation*	Number of Cases in Grp.	At 4 months: All Improvement No.	Pct.	At 4 months: Marked Impr.** No.	Pct.	At 10 months: All Improvement No.	Pct.	At 10 months: Marked Impr.** No.	Pct.	At 10 months: Relapsed No.	Pct.	At 22 months: All Improvement No.	Pct.	At 22 months: Marked Impr.** No.	Pct.	At 22 months: Relapsed No.	Pct.
	(Column No.)			(11)		(12)		(13)		(14)		(15)		(16)		(17)		(18)	
	CASES TREATED ON VA SM PROTOCOL																		
	Disease Relatively "Unmixed"** With Collapse Therapy																		
1.	"Old" Regimens**, 22 mo. F-U	IA1a	11	11	100	1	9	10	91	9	82	2	18	9	82	9	82	4	36
2.	"New" Regimens**, 10 mo. F-U	IB1a	11	11	100	5	45	11	100	11	100	1	9	—	—	—	—	—	—
	Without Collapse Therapy																		
3.	"Old" Regimens, 22 mo. F-U	IA1b	6	6	100	2	33	5	83	4	67	1	17	5	83	5	83	1	17
4.	"New" Regimens, 10 mo. F-U	IB1b	7	7	100	1	14	7	100	3	43	0	0	—	—	—	—	—	—
	Disease "Mixed"** (Acute & Chronic) With Collapse Therapy																		
5.	"Old" Regimens, 22 mo. F-U	IA2a	1	1	100	0	0	1	100	1	100	0	0	1	100	1	100	0	0
6.	"New" Regimens, 10 mo. F-U	IB2a	2	2	100	0	0	1	50	1	50	1	50	—	—	—	—	—	—
	Without Collapse Therapy																		
7.	"Old" Regimens, 22 mo. F-U	IA2b	14	11	79	0	0	7	50	4	29	8	57	5	36	4	29	9	64
8.	"New" Regimens, 10 mo. F-U	IB2b	5	2	40	0	0	2	40	1	20	3	60	—	—	—	—	—	—
	NON-PROTOCOL CASES**																		
	Disease Relatively "Unmixed"** With Collapse Therapy																		
9.	"Old" Regimens, 22 mo. F-U	IIA1a	7	7	100	0	0	7	100	2	29	1	14	7	100	7	100	1	14
10.	"New" Regimens, 10 mo. F-U	IIB1a	1	1	100	0	0	1	100	1	100	0	0	—	—	—	—	—	—
	Without Collapse Therapy																		
11.	"Old" Regimens, 22 mo. F-U	IIA1b	8	7	88	2	25	8	100	5	63	1	12	8	100	8	100	2	25
12.	"New" Regimens, 10 mo. F-U	IIB1b	4	3	75	0	0	4	100	2	50	0	0	—	—	—	—	—	—
	Disease "Mixed"** (Acute & Chronic) With Collapse Therapy																		
13.	"Old" Regimens, 22 mo. F-U	IIA2a	2	2	100	0	0	2	100	0	0	0	0	2	100	1	50	0	0
14.	"New" Regimens, 10 mo. F-U	IIB2a	0	0	0	0	0	0	0	0	0	0	0	—	—	—	—	—	—

Without Collapse Therapy																			
15. "Old" Regimens, 22 mo. F-U	IIA2b	6	5	83	0	0	5	83	0	0	2	33	3	50	0	0	4	67
16. "New" Regimens, 10 mo. F-U	IIB2b	1	1	100	0	0	0	0	0	0	1	100	—	—	—	—	—	—
SUB-TOTALS																			
PROTOCOL CASES																			
Disease Relatively "Unmixed"																			
17. With Collapse Therapy	I1a	22	22	100	6	27	21	95	20	91	3	14	—	—	—	—	—	—
18. Without Collapse Therapy	I1b	13	13	100	3	23	12	92	7	54	1	8	—	—	—	—	—	—
Disease "Mixed" (Acute & Chronic)																			
19. With Collapse Therapy	I2a	3	3	100	0	0	2	67	2	67	1	33	—	—	—	—	—	—
20. Without Collapse Therapy	I2b	19	13	68	0	0	9	47	5	26	11	58	—	—	—	—	—	—
NON-PROTOCOL CASES																			
Disease Relatively "Unmixed"																			
21. With Collapse Therapy	II1a	8	8	100	0	0	8	100	3	37	1	12	—	—	—	—	—	—
22. Without Collapse Therapy	II1b	12	10	83	2	17	12	100	7	58	1	8	—	—	—	—	—	—
Disease "Mixed" (Acute & Chronic)																			
23. With Collapse Therapy	II2a	2	2	100	0	0	2	100	0	0	0	0	—	—	—	—	—	—
24. Without Collapse Therapy	II2b	7	6	86	0	0	5	71	0	0	3	43	—	—	—	—	—	—
PROTOCOL CASES																			
25. Disease "Unmixed" (lines 17, 18)	I 1	35	35	100	9	26	33	94	27	77	4	11	—	—	—	—	—	—
26. Disease "Mixed" (lines 19, 20)	I 2	22	16	73	0	0	11	50	7	32	12	55	—	—	—	—	—	—
NON-PROTOCOL CASES																			
27. Disease "Unmixed" (lines 21, 22)	II 1	20	18	90	2	10	20	100	10	50	2	10	—	—	—	—	—	—
28. Disease "Mixed" (lines 23, 24)	II 2	9	8	89	0	0	7	78	0	0	3	33	—	—	—	—	—	—
TOTALS																			
29. ALL PROTOCOL CASES (lines 25, 26)	I	57	51	89	9	16	44	77	34	60	16	28	—	—	—	—	—	—
30. NON-PROTOCOL CASES (lines 27, 28)	II	29	26	90	2	7	27	93	10	34	5	17	—	—	—	—	—	—
31. GRAND TOTAL—ALL CASES		86	77	90	11	13	71	83	44	51	21	24	—	—	—	—	—	—

*—Group designation symbols as follows:
I—Protocol Cases A—"Old" Regimens** 1—"Unmixed" Disease** a—with collapse therapy
II—Non-Protocol Cases B—"New" Regimens** 2—"Mixed" Disease** b—without collapse therapy
**—see text for definition and explanation
#—see text for types of collapse employed
Abbreviations: SM = streptomycin; F-U = follow-up (from start of treatment).

TABLE V. B.

RESULTS OF STREPTOMYCIN TREATMENT

Group No.	TREATMENT GROUPS	Group Designation*	EMPLOYMENT OF COLLAPSE THERAPY AFTER START OF SM TREATMENT# (During SM) 0-4 mos. No.	Pct.	(After SM Therapy) 5-10 mos. No.	Pct.	11-22 mos. No.	Pct.	SPUTUM CONVERSION BY CULTURE (Time After Start SM) At 10 mos. No.	Pct.	At 22 mos. No.	Pct.	CUMULATIVE MORTALITY FROM PULMONARY TBC (Time After Start SM) At 10 mos. No.	Pct.	At 22 mos. No.	Pct.	Group No.
	(Column No.)		(19)		(20)		(21)		(22)		(23)		(24)		(25)		
	CASES TREATED ON VA SM PROTOCOL																
	Disease Relatively "Unmixed"** With Collapse Therapy																
1.	"Old" Regimens**, 22 mo. F-U	IA1a	4	36	4	36	3	28	—	—	7	64	0	0	2	18	1
2.	"New" Regimens**, 10 mo. F-U	IB1a	8	73	3	27	—	—	9	82	—	—	0	0	—	—	2
	Without Collapse Therapy																
3.	"Old" Regimens, 22 mo. F-U	IA1b	0	0	0	0	0	0	—	—	4	67	1	17	1	17	3
4.	"New" Regimens, 10 mo. F-U	IB1b	0	0	0	0	—	—	1	14	—	—	0	0	—	—	4
	Disease "Mixed"** (Acute & Chronic) With Collapse Therapy																
5.	"Old" Regimens, 22 mo. F-U	IA2a	0	0	0	0	1	100	—	—	0	0	0	0	0	0	5
6.	"New" Regimens, 10 mo. F-U	IB2a	1	50	1	50	—	—	0	0	—	—	0	0	—	—	6
	Without Collapse Therapy																
7.	"Old" Regimens, 22 mo. F-U	IA2b	0	0	0	0	0	0	—	—	3	21	5	36	7	50	7
8.	"New" Regimens, 10 mo. F-U	IB2b	0	0	0	0	—	—	0	0	—	—	3	60	—	—	8
	NON-PROTOCOL CASES**																
	Disease Relatively "Unmixed"** With Collapse Therapy																
9.	"Old" Regimens, 22 mo. F-U	IIA1a	3	42	2	29	2	29	—	—	7	100	0	0	0	0	9
10.	"New" Regimens, 10 mo. F-U	IIB1a	1	100	0	0	—	—	1	100	—	--	0	0	—	—	10
	Without Collapse Therapy																
11.	"Old" Regimens, 22 mo. F-U	IIA1b	0	0	0	0	0	0	—	—	6	75	0	0	0	0	11
12.	"New" Regimens, 10 mo. F-U	IIB1b	0	0	0	0	—	—	4	100	—	—	0	0	—	—	12
	Disease "Mixed"** (Acute & Chronic) With Collapse Therapy																
13.	"Old" Regimens, 22 mo. F-U	IIA2a	2	100	0	0	0	0	—	—	2	100	0	0	0	0	13
14.	"New" Regimens, 10 mo. F-U	IIB2a	0	0	0	0	—	—	0	0	—	—	0	0	—	—	14

	Without Collapse Therapy																	
15.	"Old" Regimens, 22 mo. F-U	IIA2b	0	0	0	0	0	0	—	—	0	0	0	0	1	17	15
16.	"New" Regimens, 10 mo. F-U	IIB2b	0	0	0	0	—	—	0	0	—	—	0	0	—	—	16
	SUB-TOTALS																	
	PROTOCOL CASES									Latest Data								
	Disease Relatively "Unmixed"									No.	Pct.							
17.	With Collapse Therapy	I1a	12	54	7	32	3	14		16	73		0	0	—	—	17
18.	Without Collapse Therapy	I1b	0	0	0	0	0	0		5	38		1	8	—	—	18
	Disease "Mixed" (Acute & Chronic)																	
19.	With Collapse Therapy	I2a	1	33	1	33	1	33		0	0		0	0	—	—	19
20.	Without Collapse Therapy	I2b	0	0	0	0	0	0		3	16		8	42	—	—	20
	NON-PROTOCOL CASES																	
	Disease Relatively "Unmixed"																	
21.	With Collapse Therapy	II1a	4	50	2	25	2	25		8	100		0	0	—	—	21
22.	Without Collapse Therapy	II1b	0	0	0	0	0	0		10	83		0	0	—	—	22
	Disease "Mixed" (Acute & Chronic)																	
23.	With Collapse Therapy	II2a	2	100	0	0	0	0		2	100		0	0	—	—	23
24.	Without Collapse Therapy	II2b	0	0	0	0	0	0		0	0		0	0	—	—	24
	PROTOCOL CASES																	
25.	Disease "Unmixed" (lines 17, 18)	I 1	12	34	7	20	3	9		21	60		1	3	—	—	25
26.	Disease "Mixed" (lines 19, 20)	I 2	1	5	1	5	1	5		3	14		8	36	—	—	26
	NON-PROTOCOL CASES																	
27.	Disease "Unmixed" (lines 21, 22)	II 1	4	20	2	10	2	10		18	90		0	0	—	—	27
28.	Disease "Mixed" (lines 23, 24)	II 2	2	22	0	0	0	0		2	22		0	0	—	—	28
	TOTALS																	
29.	ALL PROTOCOL CASES (lines 25, 26)	I	13	23	8	14	4	7		24	42		9	16	—	—	29
30.	NON-PROTOCOL CASES (lines 27, 28)	II	6	21	2	7	2	7		20	69		0	0	—	—	30
31.	GRAND TOTAL—ALL CASES		19	22	10	12	6	7		42	49		9	10	—	—	31

*—Group designation symbols as follows:
I—Protocol Cases A—"Old" Regimens** 1—"Unmixed" Disease** a—with collapse therapy
II—Non-Protocol Cases B—"New" Regimens** 2—"Mixed" Disease** b—without collapse therapy
**—see text for definition and explanation
#—see text for types of collapse employed
Abbreviations: SM = streptomycin; F-U = follow-up (from start of treatment).

groups. Sputum is converted by culture (columns 22 and 23) in 60 per cent of the "unmixed" cases, and in 14 per cent of the "mixed" cases, according to the latest data available. Mortality from pulmonary tuberculosis (columns 24 and 25) is very much higher for the "mixed" cases (36 per cent of 22 cases at 10 months, 47 per cent of 15 cases at 22 months) than it is for the "unmixed" cases (3 per cent of 35 cases at 10 months, 18 per cent of 17 cases at 22 months).

Collapse therapy (columns 19 to 21) was employed in 22 (63 per cent of the 35 "unmixed" cases, and in 3 (18 per cent) of the 22 "mixed" cases, or in a total of 25 (44 per cent) of the 57 protocol cases. The types of collapse therapy employed, and the time of their employment, were as follows:

Period After Start of SM Therapy	"UNMIXED" CASES			"MIXED" CASES		
	Thoracoplasty	Pneumothorax	Pneumoperitoneum and/or phrenic	Thoracoplasty	Pneumothorax	Pneumoperitoneum and/or phrenic
0- 4 mos.	6	3	3	1	0	0
5-10 mos.	5	1	1	1	0	0
11-22 mos.	3	0	0	1	0	0
TOTALS	14	4	4	3	0	0

The small number of cases does not permit an extensive breakdown of results according to the variables of type of collapse and time introduced. In the group of 11 cases on the "new" regimens with "unmixed" disease receiving collapse therapy (Group 2, Table V), where collapse was introduced earlier than in any other protocol group (in eight cases during the four-month treatment period), there is the highest percentage (82 per cent) of conversion of sputum by culture of any group. Artificial pneumothorax, when successfully introduced, seemed to contribute as much to the overall result as thoracoplasty; and pneumoperitoneum and/or temporary phrenic paralysis, in selected instances, proved to be approximately as effective.

Of particular interest is the comparison of the "unmixed" protocol cases, with and without collapse therapy (Groups 17 and 18). Those receiving collapse therapy (Group 17) were less far-advanced, less frequently cavernous, and less predominantly exudative than those not receiving collapse therapy (Group 18), and these differences must be taken into account. Yet both groups had 100 per cent x-ray improvement four months after the start of therapy, and over 90 per cent 10 months after the start of therapy; marked x-ray improvement, however, while about the

same (about 25 per cent) at four months, occurred in 91 per cent of cases receiving collapse therapy, at 10 months after the start of treatment, but in only 54 per cent of those not receiving collapse therapy at this same point in time. Sputum conversion, according to latest data available, was 73 per cent for the group receiving collapse therapy, 38 per cent for the group not receiving it.

Comparison of the two "mixed" groups, those receiving collapse therapy and those not (Groups 19 and 20), is less valid because of the small number of cases (three) in the former group. Approximately the same differentials are noted, however, in favor of the group receiving collapse therapy (Group 19) as in the case of the "unmixed" groups.

Non-Protocol Cases

As a group the cases of active pulmonary tuberculosis which received streptomycin therapy primarily for extra-pulmonary tuberculosis, designated as the "non-protocol" group (Group 30 in Table V), differ significantly from the protocol cases (Group 29) in the defining characteristics listed in Table V-A (columns 1 to 8). The non-protocol cases are far-advanced in 55 per cent and moderately advanced in 38 per cent of 29 cases; the protocol cases are far-advanced in 88 per cent, moderately advanced in 12 per cent of 57 cases. Non-protocol cases had pre-streptomycin progressive disease in 24 per cent and stationary disease in 69 per cent; protocol cases had progressive disease in 72 per cent and stationary disease in 23 per cent. Non-protocol cases had cavities demonstrable in 59 per cent, protocol cases in 75 per cent. Non-protocol cases had predominantly exudative disease in only 24 per cent, protocol cases in 79 per cent. The two groups are therefore so different that the effects of streptomycin therapy in the non-protocol cases will be studied separately from those in the protocol cases.

The 29 non-protocol cases may be divided into "unmixed" (Group 27, Table V) and "mixed" cases (Group 28), as were the protocol cases. The "mixed" cases (nine in number) are more far-advanced, more progressive (before streptomycin), more cavernous, and more predominantly exudative than the "unmixed" (20 in number).

It is observed (Table V-B) that both groups had approximately the same percentage of all degrees of x-ray improvement (90 and 89 per cent) at the end of the four-month treatment period (column 11); at the end of the first follow-up period, however, the percentage of improvement (column 13) was 100 per cent for the "unmixed" cases and 78 per cent for the "mixed" group; 22 months after the start of treatment (column 16) it was 100 per cent for the 15 "unmixed" cases (Groups 9 and 11), 63 per cent for the

eight "mixed" cases (Groups 13 and 15) followed to this point. The corresponding figures for marked x-ray improvement (columns 12, 14 and 17) are: for "unmixed" cases (Group 27), 10 per cent at four months, 50 per cent at 10 months, and 100 per cent at 22 months after the start of therapy; for "mixed" cases (Group 28), 0 per cent at four months, 0 per cent at 10 months, and 12 per cent at 22 months after the start of treatment. Relapse rates at 10 and 22 months after the start of treatment (columns 15 and 18) are correspondingly definitely higher for the "mixed" than for the "unmixed" cases.

Collapse therapy (columns 19 to 21, Table V) has been employed in eight of the 29 non-protocol cases (34 per cent, contrasted with 44 per cent of the protocol cases): in eight of 20 (40 per cent) of "unmixed" cases (Groups 21 and 22), and two of nine (22 per cent) of "mixed" cases (Groups 23 and 24). Types of collapse and time of employment in these 10 cases of collapse therapy were:

Period After Start of SM Therapy	"UNMIXED" CASES			"MIXED" CASES		
	Thoraco-plasty	Pneumo-thorax	Phrenic	Lobec-tomy	Thoraco-plasty	Phrenic
0- 4 mos.	3	0	1	0	1	1
5-10 mos.	1	1	0	0	0	0
11-22 mos.	1	0	0	1	0	0
TOTALS	5	1	1	1	1	1

With an even smaller number of cases receiving collapse therapy in the non-protocol group than in the protocol group, it is not possible to draw valid conclusions as to the effect of type of collapse or the time of its employment.

Comparison of the "unmixed" groups treated with and without collapse therapy (Groups 21 and 22, Table V) results in much the same impression of more favorable results for the former (with collapse therapy) as in the case of the protocol cases. Both groups have sputum conversion rates (100 and 83 per cent respectively) higher than corresponding groups (Groups 17 and 18) treated on the pulmonary tuberculosis protocol (73 and 38 per cent respectively). Only one patient of the non-protocol series, in the "mixed" group without collapse therapy (Group 15), has died, between 11 and 22 months after the start of treatment.

Thus it is seen, in the non-protocol cases—admittedly different in many respects from the protocol cases—that the same *relative* differences occur between "mixed" and "unmixed" groups, with and without collapse therapy, as occur in the protocol cases. This

applies generally to all the observations listed in Table V-B: x-ray improvement, relapse rates, sputum conversion, and mortality from pulmonary tuberculosis.

Discussion

The study of the effects of streptomycin therapy in the treatment of tuberculosis, having passed through the stages of establishing its therapeutic efficacy, avoiding the unnecessarily high incidence of toxicity of the larger dosages, and the unnecessarily high rates of emergence of streptomycin - resistant strains of tubercle bacilli obtained with regimens of too long duration, is now in the more difficult stage of attempting to establish the more precise indications for the use of streptomycin as a part of the overall program of treatment of cases of tuberculosis. It has become increasingly important to determine the types of disease which respond best, as well as the indications for the use of streptomycin in cases where its contribution to a favorable result may be expected to be less striking.

These problems are particularly acute in the treatment of pulmonary tuberculosis. More information is urgently needed especially with respect to the timing of combined streptomycin and collapse therapy. And more data are needed as to the indications for streptomycin therapy according to the type of pulmonary tuberculosis which a patient may have. It is believed that the type of analysis of the experience of the Minneapolis Study Unit here presented may be of assistance in answering these questions.

Methods of classification and evaluation are inseparable parts of the problem. It is believed that the methods of classification ordinarily employed—stage or extent of the disease, estimates of the amount of "exudation," and observations as to the cavitary component—are insufficient for adequate evaluation. Other identifying variables, such as age of the lesion, x-ray observations of confluence, density, and character of a cavity wall, probably all must be taken into account, and in the study of the Veterans Administration, Army and Navy, through the medium of the individual case reports now being collected for analysis, it is hoped that useful information as to the relative importance of these, and more, will be forthcoming.

The experience of the Minneapolis Veterans Administration Hospital has led to the belief that a classification of considerable usefulness concerns an estimate of the acuteness of the inflammatory tuberculous process (from both x-ray and clinical data), particularly as to whether there is present a clear-cut mixture of components which may be designated as chronic, and acute or subacute. In this "mixed" type of case—that with well defined

chronic lesions plus lesions of more recent origin, especially if fibrocavernous disease is present—the outlook, with or without streptomycin, is entirely different from that of the relatively "unmixed" case—that in which the lesions are predominantly acute or subacute, with little or no chronic component. In our experience the recognition of this factor in classification has been more meaningful than almost any other variable.

The problems of evaluation of results are very real, and fully as difficult and as important as those of classification.

"It probably is not an unfair statement to say that no uniform or standard method of reporting results of treatment of any form of tuberculosis has been devised. There is not agreement as to what criteria are the most important, or relatively most important. The usual appraisal is a composite of a number of clinical observations, such as roentgenographic change, sputum examination, clinical signs, and erythrocyte sedimentation rate. In the final analysis *survival without detectable reactivation of the disease under essentially "normal" socio-economic conditions* is the criterion for success of therapy. But obviously there are gradations of efficacy short of this end result which are recognized as satisfactory, and such a criterion, if solely relied upon, cannot be applied until many years have passed."[6]

In most studies of the effect of streptomycin in the treatment of pulmonary tuberculosis primary reliance has been placed on x-ray improvement and sputum conversions as the best criteria for the success of therapy. Improvement in such clinical signs as disappearance of fever, reduction in sputum volume, an improved general sense of well-being, and weight gain, has been found to be somewhat illusory. No study has yet been followed long enough to establish clearly mortality rates, although it is possible that the application of actuarial life table techniques may even now afford valuable mortality data of differential value.

There can be little quarrel with the validity of sputum conversion as an index of therapy of which streptomycin may be a part. The fact of "x-ray improvement," however, is more debatably a reliable criterion. Most studies have placed heavy reliance on a comparison of x-rays taken at the start of treatment and at the end of the treatment period, and have tabulated results as improved, unchanged, or worse. Such a method has the great advantage of relative accuracy, but disregards the *degree* of change, which it is believed is fully as important. The cooperative study of the Veterans Administration, Army and Navy, in its latest report,[8] has emphasized the desirability of taking into account the degree of change, and has attempted to standardize a method of determining this with relative objectivity.

In the 86 cases presented in this report, for example (bottom

line of Table V), it is seen that 90 per cent were observed to have all degree of x-ray improvement (column 11). This figure was almost identical for the cases treated on the pulmonary protocol, primarily for acute and progressive pulmonary tuberculosis (Group 29), and for the cases treated primarily for extra-pulmonary tuberculosis but with active pulmonary tuberculosis present (Group 30), in spite of the fact that the two groups are found to differ markedly in most important characteristics (Table V-A). If all degrees of x-ray improvement are determined also 10 and 22 months after the start of treatment (columns 13 and 16, Table V-B), the difference between Groups 29 (protocol) and 30 (non-protocol) becomes more apparent. But it has been our experience that determining the frequency of *marked* x-ray improvement (columns 12, 14 and 17) is a better measure of the effect of streptomycin than the simpler determination of any degree of improvement.

In reporting such observations as x-ray change, the incidence of relapse, sputum conversion, and mortality, it is believed that it is important to base these on a single point in time, usually or nearly always the day of starting specific therapy. It is believed that such a technique is preferable to recording changes separately for different observation periods, with different basing points (as, for example, "change in follow-up period," which compares between end of treatment and latest follow-up data available, but makes possible no precise comparison with the start of treatment), and will permit simpler and more accurate statistical analysis of results.

It is apparent from the analysis presented that streptomycin-treated cases receiving collapse therapy in addition to the antibiotic differ from those not receiving collapse therapy. This probably is inevitable, because of the well-established indications and contraindications for collapse therapy, but it does make difficult precise statistical comparison of the groups treated with and without collapse. In general, two groups do not receive collapse therapy: those less advanced where the indications are absent or slight, and those very advanced where collapse would be desirable but in which it is impossible or questionably possible to induce collapse, for a variety of reasons.

Many of the cases in this study classed as "unmixed" acute or subacute cases, even with a cavitary component, responded so well to streptomycin therapy that collapse therapy was not indicated, yet the majority (22 of 35 protocol cases) did receive collapse, usually on the indication that the cavitary component was unlikely to heal without such adjunctive therapy. Among the "mixed" protocol cases, those with both chronic and acute

or subacute disease, on the other hand, collapse therapy was induced in only three of 22 cases.

The evidence is becoming increasingly clear that in all cases with cavitary components, where streptomycin therapy of itself is unlikely to achieve cavity closure, collapse therapy should be added at a relatively early date, if serious relapse is to be avoided and the best opportunity for collapse not lost. In chronic cases our experience has been that the improvement is slight, less than that in acute and subacute cases, but definite, up until approximately eight months after the start of streptomycin treatment, after which relapses become increasingly serious.[10] The "mixed" cases as here defined present a combination of these problems: more improvement than "relatively unmixed" chronic cases, because of the effect of the antibiotic on the acute or subacute component present; but early relapse even earlier than in "unmixed" chronic cases, probably related to the fibro-cavernous component which is relatively uninfluenced by the antibiotic therapy.

The kind of case of pulmonary tuberculosis here designated as "mixed" is of course the primary therapeutic problem of almost every institution charged with the care of tuberculous patients. Streptomycin therapy can and does help these patients, but unfortunately only temporarily in a considerable proportion, unless other therapeutic measures, especially collapse therapy, are available and introduced promptly. One may indeed speculate whether if collapse therapy were employed more frequently and more intimately in association with the period of primary benefit from streptomycin, the relapse and mortality rates would not be lower than indicated, and superior overall results achieved, in this group.

The New York State Hospitals group has published a careful analysis of their experience with streptomycin in the treatment of pulmonary tuberculosis, with particular reference to the integration of collapse therapy with streptomycin therapy.[12] Their analysis has indicated the broadened indications for collapse therapy with the use of streptomycin, and the desirability of planning the two forms of therapy as a combined program. The New York State Hospitals experience has also been reported according to the variables of acute, subacute, and chronic pulmonary disease, but has not stressed the special problem of the "mixed" case, emphasized in this presentation.

Because of the different way in which different pulmonary tuberculous problems respond to streptomycin therapy, the overall results reported for a series will depend considerably on the make-up of the series reported. More recent disease, more acute, less advanced, less cavernous, has results of therapy far superior to those of older, more chronic and far-advanced disease, partic-

ularly of the variety here classified as "mixed" chronic and acute. The size of this particular classification in any series treated probably influences the overall result more than almost any other factor.

Many other variables in the streptomycin therapy of pulmonary tuberculosis have not been mentioned in this report. The race of the patients has not been discussed, although it undoubtedly is a factor. Emergence of streptomycin-resistant strains, use of retreatment with streptomycin, the role of bed rest itself, and probably other important factors, have undoubtedly entered into the results presented. This report has rather attempted to concentrate on certain classification variables, and on a careful method of reporting results, as one approach to the complex problem of evaluation of the results of streptomycin therapy of tuberculosis.

SUMMARY

1) The experience of the cooperative study by the Veterans Administration, Army and Navy of the effects of streptomycin in the treatment of tuberculosis has been briefly reviewed. This investigation has been one primarily of the influence of varying dosage regimens in quite uniform clinical material. It has shown that dosages of 1 gram a day are therapeutically effective, with an incidence of toxic manifestations sufficiently low not to be a serious handicap. It has shown that regimens of 42-day and 60-day duration, while not quite as effective as those of longer duration, are preferable to the latter because of definitely lower incidence of emergence of streptomycin-resistant tubercle bacilli.

2) The method of reporting data in the study of the Veterans Administration, Army and Navy has permitted relatively little evaluation of variables of therapy other than those of regimen. To a limited extent the study has indicated that results are superior when streptomycin and collapse therapy are employed in combination; that disease which is progressive before initiation of streptomycin therapy improves more than stationary disease; and that moderately advanced disease improves more than minimal or far-advanced disease, in comparable periods of time.

3) The experience of the Minneapolis Veterans Administration Hospital with the streptomycin therapy of cases of pulmonary tuberculosis is presented. The material consists of 86 cases of active disease, 57 cases treated according to the Veterans Administration protocol for pulmonary tuberculosis, and 29 cases of less extensive disease treated primarily for extra-pulmonary tuberculosis.

4) All cases had a definitely acute or subacute inflammatory tuberculous component; a proportion of these had clear-cut mix-

tures of both chronic disease and more recent disease. This "mixed" group of cases was found to have an outcome of therapy definitely inferior to that of the "relatively unmixed" acute and subacute cases, in all categories studied. It is believed that it is important to stress this classification in the evaluation of the results of streptomycin therapy in the treatment of tuberculosis.

5) In the 86 cases, both those treated and not treated on the pulmonary protocol, results were superior when collapse therapy (thoracoplasty in over half the cases collapsed) was employed in close conjunction with the period of maximum benefit from streptomycin therapy, which in general consisted of the first eight months after the start of antibiotic therapy. This was true for both "relatively unmixed" acute and chronic cases and for "mixed" cases, but especially for the latter. These observations appear to be largely independent of variations in the five streptomycin regimens employed.

6) Evidence is presented to indicate that observation of any degree of x-ray improvement, whether slight, moderate or marked, at the end of the initial treatment period, is a method of evaluation which is inadequate for discrimination of results between regimens employed, or between groups of cases treated. It is believed that standardized measures of the degree of x-ray improvement enhance roentgenographic evaluation, particularly in the first months after the start of therapy. Sputum conversion rates and relapse rates are important additional criteria for evaluating results. In later follow-up periods mortality rates are of increasing value.

7) It is concluded that the response of the cavitary component to streptomycin therapy, as to any form of treatment of pulmonary tuberculosis, is the chief factor determining the outcome of a program of therapy in which streptomycin is a part; and that prompt and energetic measures directed toward the control of that component have at present the best opportunity for improving still further the already distinguished achievements of the streptomycin therapy of pulmonary tuberculosis.

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REFERENCES

1 Riggins, H. McL. and Hinshaw, H. C.: "Streptomycin-Tuberculosis Research Project of the American Trudeau Society," *Am. Rev. Tuberc.*, 59:140, 1949.

2 Riggins, H. McL. and Hinshaw, H. C. (editors): "Streptomycin and Dihydrostreptomycin in Tuberculosis," *National Tuberculosis Association*, New York, 1949 (Sections V and VI, pp. 107-402).
3 Streptomycin Committee, Central Office, Veterans Administration: "The Effect of Streptomycin Upon Pulmonary Tuberculosis: Preliminary Report of a Cooperative Study of 223 Patients by Army, Navy, and Veterans Administration," *Am. Rev. Tuberc.*, 56:485, 1947.
4 Streptomycin Committee: "The Effects of Streptomycin on Tuberculosis in Man, Report to the Council on Pharmacy and Chemistry," *J.A.M.A.*, 135:634, 1947.
5 Streptomycin Committee: "Streptomycin in the Treatment of Tuberculosis: Current Status, Report to the Council on Pharmacy and Chemistry," *J.A.M.A.*, 138:584, 1948.
6 Tucker, W. B.: "Evaluation of Streptomycin Regimens in the Treatment of Tuberculosis: An Account of the Study of the Veterans Administration, Army and Navy, July 1946 to April 1949," *Am. Rev. Tuberc.*, (to be published).
7 Tucker, W. B.: "Evaluation of Different Streptomycin Regimens in the Treatment of Tuberculosis: Summary of the Study of the Veterans Administration, Army and Navy, July 1946 to April 1949," *Minutes of the Seventh Streptomycin Conference,*[8] *Veterans Administration*, Washington, D. C., p. 171, 1949.
8 *Minutes of the Seventh Streptomycin Conference, April 21-24, 1949*, Denver, Colorado, edited by Veterans Administration Area Office, Tuberculosis Section, Washington, D. C. (Table 1, pp. 39-76).
9 Amberson, J. B.: Summary Discussion of Table 1—"Pulmonary Tuberculosis," *Minutes of the Seventh Streptomycin Conference,*[8] *Veterans Administration*, Washington, D. C., p. 80, 1949.
10 Tucker, W. B. and Falk, A.: "Possible Additional Indications for the Streptomycin Treatment of Pulmonary Tuberculosis," *Minutes of the Seventh Streptomycin Conference,*[8] *Veterans Administration*, Washington, D. C., p. 100, 1949.
11 Medlar, E. M.: "The Pathogenesis of Minimal Pulmonary Tuberculosis: A Study of 1,225 Necropsies in Cases of Sudden and Unexpected Death," *Am. Rev. Tuberc.*, 58:583, 1948.
12 Riggins, H. McL., Horton, R., Lincoln, N. S., Hainlen, E. E. and Monroe, J.: "The Integration of Streptomycin Therapy with Other Procedures in the Treatment of Tuberculosis," *in* "Streptomycin and Dihydrostreptomycin in Tuberculosis," *N.T.A.*, New York, 1949.[2]

Streptomycin in the Treatment of Tuberculosis in Children*

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Streptomycin has been developed into an extremely important place in the treatment of tuberculosis. The medical literature is replete with articles dealing with streptomycin in the treatment of tuberculosis in adults but few articles have appeared concerning the use of this antibiotic in treating tuberculosis in children. Because of the tendency of the past 15 years to pay less attention to the child with primary tuberculosis and to close many of the previously well-occupied children's units in sanatoria throughout the country, it might be expected that streptomycin would find a very insignificant role in this phase of tuberculosis work. However, there are still children with more than the simple primary tuberculosis who require more than an occasional clinic checkup while on a limited exercise routine at home: there are still a fair number of children whose tuberculosis is not confined to hilar nodes, who require sanatorium care and definite therapy. It is these children who provide a place for the use of streptomycin.

At Maybury Sanatorium Children's Unit, streptomycin was made available for emergency cases in April 1947, for research purposes in August 1947, and for all purposes in October 1947. From April 22, 1947 to January 31, 1949, 101 of our 281 children received streptomycin. A review of these children with five months' follow-up in comparison with a similar series comprising 780 children treated in the six-year period from January 1, 1941 to December 31, 1946, forms the basis for this presentation. There is no essential difference in the treatment of the two groups except that streptomycin was used in the 1947-49 group. The same system of classification and the same method of evaluating the results was used in both groups. Streptomycin was not used in the simple primary tuberculosis cases because they have a tendency to recover without treatment and the hazards of streptomycin therapy did not justify its use. The 101 cases treated with streptomycin are divided roughly into the following groups: 1) miliary and meningitis, 2) severe primary, 3) primary with bronchial complication (PBC), 4) reinfection tuberculosis, and 5) extrapulmonary tuberculosis. Streptomycin therapy varied in the different groups and several changes in dosage were made during the period of this study. Of the 101

*From the Wm. H. Maybury Sanatorium, Northville, Michigan.

children, 22 had part or all of their streptomycin before transfer to Maybury Sanatorium. We are not presuming to outline the ideal method of using streptomycin but are merely presenting our observation of 101 streptomycin- treated tuberculosis children and describing our present method of administration.

Miliary and Meningeal Tuberculosis

Miliary and meningeal tuberculosis constituted the emergency cases for which the early supply of streptomycin was hopefully allocated. It has been noted that this form of tuberculosis provided a prime indication for streptomycin therapy.[1,2] Infrequently had there previously been recovereis observed. Of the 50 miliary cases treated during the 1941-46 period only 13 recovered. The recoveries here occurred only in the coarse type but never in the fine miliary cases. Although the fine miliary cases are more likely to develop meningitis it was found to be a common occurrence also in children with coarse miliary lesions.

Miliary tuberculosis is prone to develop in the severe primary and the progressive primary type of case. The sooner streptomycin therapy can be instituted the better are the chances of good results. Even in those children who are potential miliary cases and who show a definite aggravation of toxemia without obvious cause, one should suspect beginning miliary spread and institute streptomycin therapy. Children, even very young children, tolerated streptomycin well—better than adults.

Large doses of streptomycin are indicated in miliary and meningeal tuberculosis. After early schedules were modified by reason of our experience and information received from other workers in the field,[3,4] a dosage formula based upon body weight was developed. For miliary tuberculosis it is as follows: 55 to 88 mg. streptomycin per kilogram (25 to 40 mg. streptomycin per pound) per day for three to six months depending upon the occurrence of a definite recession of the disease and then 25 to 44 mg. per kilogram (10 to 20 mg. per pound) per day for the remainder of the six months period. The severity of the case is used to determine the exact dosage within the formula. The daily amount is divided into two or three doses depending upon the quantity of solution to be injected at each time and the size of the patient. Our standard streptomycin solution is 200 mg. to 1 cc. of water: 1.5 cc. is about the maximum injection which a small child will tolerate.

Six questionable miliary* cases were also treated and four of

*Miliary tuberculosis was classified as questionable when the roentgenogram taken at the clinical onset of the miliary episode showed fairly well defined miliary lesions which were not confirmed by subsequent roentgenograms, streptomycin having been administered in the meantime.

these have no response to the caloric test. These 18 children are alive and doing well. All have completed their course of streptomycin and gastric cultures are negative for acid fast bacilli. Three of the miliary and four of the questionable miliary cases have been discharged to their homes. Three children whose miliary lesions were advanced were left with miliary fibrotic nodules but without accompanying clinical manifestation of miliary tuberculosis. Relatively few acute toxic manifestations were experienced in this group but lack of nystagmus to the caloric test developed in nine of the 12 miliary cases treated and five of these nine also had objective evidence of dizziness.

Meningitis

Four additional cases of miliary tuberculosis were given streptomycin therapy but there was an associated meningitis and these cases are considered with the nine children who comprise the meningitis group. Two of these developed meningitis while they were under streptomycin therapy for miliary tuberculosis. One of these had an extremely fine miliary and normal spinal fluid when intramuscular streptomycin was started. After meningitis developed he was given intrathecal streptomycin in addition to the intramuscular; the total course covered a six months period. The other child was admitted at one year of age with an advanced but coarser miliary superimposed upon a consolidated upper lobe which was excavating. Spinal fluid was normal at the beginning of streptomycin therapy. Three months later intra-thecal streptomycin was added but was not well tolerated. The intramuscular dose was increased from 60 to 96 mg. per kilogram per day. She had 151 gm. of intramuscular streptomycin in 249 days and 312 mg. of intrathecal streptomycin in 156 days. The miliary lesions became fibrotic, the pneumonic process improved but the spinal fluid findings remained positive for tuberculous meningitis and the cultures continued to be intermittently positive for acid fast bacilli. She was able to stand in her crib and take fluids until a week before she died although irritability, vomiting, and weight loss were progressive. Opisthotonos and increasing elevation of temperature up to 109 degrees F., terminal fever developed and death occurred seven months after the onset of meningitis and ten months after the start of streptomycin therapy. Of the 101 streptomycin treated children this is the only one who died at Maybury Sanatorium.

Besides the four meningitis patients who had associated miliary tuberculosis, three other children had associated extrapulmonary tuberculosis and two had associated active primary tuberculosis. In only one of these nine children were the symptoms of menin-

gitis severe when streptomycin was started. He was irrational on transfer from a general hospital. One other was admitted to the sanatorium with an advanced miliary and early meningitis. The other seven developed meningitis while in the sanatorium and streptomycin therapy was instituted before the symptoms had reached the stage that one would ordinarily have suspected the disease. The diagnosis of tuberculous meningitis was in all cases confirmed by laboratory tests on the spinal fluid.

After some variation of dosage in the early cases the following formula of streptomycin therapy was established for tuberculous meningitis: i.e., intramuscularly 55 to 88 mg. per kilogram of body weight per day for four to six months depending on the clinical and spinal fluid response and then 22 to 44 mg. per kilogram per day for the remainder of the six months period. Intrathecal streptomycin 2.5 mg. per kilogram per day (up to 50 mg.) is given for three weeks, then the same dose three times per week for three months, and then one-half that dose twice a week for two months. If intrathecal streptomycin could not be given the intramuscular dose was increased to 100 mg. per kilogram per day. The intrathecal injections were given after the spinal pressure had been reduced to normal by withdrawal of fluid, the proper amount of streptomycin was injected in 5 cc. of water.

Five children, now 26 to 19½ months after the onset of meningitis, have recovered and gone home. One, as mentioned above, is deceased. The three who remain in the sanatorium are free from symptoms and spinal fluid findings of meningitis. All have completed the streptomycin course. One child who had associated tuberculosis of the dorsal spine received no intrathecal streptomycin and two others had less than 10 intrathecal doses. All nine children have loss of equilibrium by the caloric test but have compensated well. One child, the first case, became deaf.

There is still some controversy over the use of intrathecal streptomycin in treating cases of tuberculous meningitis, one argument against its use being that streptomycin is a very irritating substance and, therefore, likely to produce neural damage. However, it is known that meningitis develops in children receiving streptomycin by intramuscular injection—two such cases are included in this series—therefore, it would seem that something more than intramuscular streptomycin was needed in treating the condition. Levinson reports 11 deaths in 19 children treated by intramuscular streptomycin alone.[5]

In the series of cases treated prior to streptomycin 39 had meningitis and all 39 died within a month after the condition was diagnosed. There is no possibility of comparing the condition of these recovered meningitis children with those not treated with

streptomycin and, therefore, it may be that at least some of the neural damages are due to the meningitis and not altogether to the drug. In our experience there is also no evidence to support the claim that intrathecal streptomycin produces either a greater incidence or a more profound type of vestibular damage than large intramuscular doses alone.

Severe Primary Tuberculosis

Severe primary tuberculosis with extensive parenchymal involvement in small children provides a definite indication for streptomycin therapy. The simple primary cases have a tendency to recover spontaneously. They can well be handled in the home. Streptomycin is not indicated in these children but they must be followed carefully for signs and symptoms of exacerbations of the primary or complications such as miliary, bone and joint, or other tuberculosis. The child who has primary tuberculosis and symptoms of pneumonia may have either a superimposed non-tuberculous infection or an acute increase in his tuberculosis. If a trial of penicillin and other measures does not result in prompt clinical and x-ray improvement one should not hesitate to start streptomycin. The formula for therapy in these cases is as follows: 33 to 66 mg. per kilogram of body weight per day for four to seven days or until there has been a satisfactory effect, then one-half that dosage three days a week for the balance of 42 doses. The determination of the number of daily doses and the size of the individual injection is made again on the basis of the size of the child and the maximum dose of a 200 mg. per cc. solution which he would tolerate. The response to streptomycin will in most cases be quite prompt so that after four to seven days the initial concentrated therapy may be reduced. Even though the clinical progress may be excellent, one must not forget the possibility of these cases developing miliary or meningeal tuberculosis and must keep constantly on the watch for signs of these complications.

Five children having severe primary tuberculosis and ranging in age from two to six months were treated with streptomycin. Some received as high as 250 mg. per kilogram per day. Only one of the five has a completely normal response to the caloric test but all have normal hearing. Three have gone home and they seemed well compensated at the time. One of the two children still in the sanatorium is well compensated but the other who was the one receiving 250 mg. per kilogram is now 14 months of age, will undoubtedly have some difficulty when he starts to walk. With our present dosage we might well have prevented this vestibular damage and still have had the tuberculosis run a favorable course.

Primary with Bronchial Complications (PBC)

Nearly 20 per cent of children admitted to Maybury Sanatorium present the dense, homogeneous, lobular, or lobar shadow of the so-called epituberculosis. This x-ray appearance is due to the combination of a large, active, primary, parenchymal focus, tuberculous, peri-bronchial lymph nodes, and some bronchial interference to pulmonary aeration and drainage. Post-mortem examinations of some of these children, dying of miliary and meningeal tuberculosis, demonstrated the bronchial factor as did bronchoscopic examination in many cases.[6]

In 1941 an analysis was made at Maybury Sanatorium of 42 of these children[6] who were examined bronchoscopically. Thirty-one, or 74 per cent, were found to have involvement of the bronchi in one or more of the following forms: extrinsic pressure from enlarged lymph nodes, tuberculoma, ulceration, edema, and redness. Decreased ciliary action in the abnormal bronchus and weak expulsive power in the poorly aerated lung distally may allow the secretions to become inspissated and to act as a plug. In five cases a caseous lymph node draining through a bronchial sinus was observed. Sputum (gastric cultures) of 30 children contained tubercle bacilli and usually this persisted over many months. Forty-one had a positive tuberculin test (one not tested). All showed enlargement of the hilar lymph nodes by x-ray. Thirty-five per cent had the left lung and 65 per cent the right lung involved; the left upper and the right upper and middle lobe were most often involved. The involved lobe was of normal size in 45 per cent, smaller than normal in 50 per cent, and larger than normal in five per cent of the cases. Other than wheezing, most children presented almost no protracted symptoms during the long course of x-ray clearing unless marked progression of the parenchymal lesion, and/or extension by bronchial, lymphatic, or hematogenous routes occurred. Twenty-eight per cent of these 42 children were dead at the end of a ten-year period.

Even children in this group who had a relatively uneventful course were found to have more residual damage than had been suspected by the eventual clearing of the x-ray. In 1945, a bronchographic study was made of 34 children having the above mentioned x-ray, clinical, and bronchoscopic history.[7] Bronchiectasis was demonstrated in 24, or 70 per cent of them. It was confined to the lobule, or lobe, which was the site of the previously observed primary disease, and extended from the hilum to the periphery. Twenty-two of these children with only lobular involvement had presented no obvious symptoms of bronchiectasis while one with involvement of the entire middle lobe and the antero-

lateral segment of the right upper lobe had experienced only occasional bouts of fever and cough but had rales over the affected area most of the time. The other child with involvement of the entire right lung had repeated severe attacks of pneumonitis.

Because of the tendency of these lesions to spread, the high percentage of deaths, and the incidence of bronchiectasis in the affected areas it was desirable to investigate the use of streptomycin in the early treatment of this type of case. In August 1947, the American Trudeau Society provided streptomycin for this purpose. Nineteen children were placed in this research group. All had the typical x-ray findings of large hilar lymph nodes and lobar, or lobular, consolidation; 14 had positive sputum cultures at the beginning of streptomycin. In 17 bronchoscopic examination was done; 11 were found to have narrowing of the bronchial lumen and six only excessive secretions. The mean dosage formula used in these cases was as follows: 30 mg. streptomycin per kilogram body weight per day given in three equal injections daily for a period of three months. Table I shows the comparison of these 19 Trudeau-Streptomycin-treated children with 26 similar cases admitted to Maybury Sanatorium during the year 1941.

The results seemed good enough that 16 subsequent children

TABLE 1

EVALUATION OF STREPTOMYCIN IN PRIMARY TUBERCULOSIS WITH BRONCHIAL COMPLICATION

A. Control Series: 101 children admitted to Maybury 1941 (12 mo.) plus 6 year follow-up.

B. Streptomycin Series: 164 children in Maybury 8-1-47 to 2-13-48 (6½ mo.) plus 13½ mo. follow-up. Average and mean dose, 30 mg/kilo/day for three months.

	A. CONTROL		B. STREPT.	
No. with typical x-ray	26		19	
No. bronchoscoped	15		17	
1. Redness and secretions only		3 (20%)		6 (35%)
2. Encroachment on lumen visible		12 (75%)		11 (65%)
Parenchymal clearing of more than 50%:				
1. in three months	7	(29%)	8	(42%)
2. in six months	11	(48%)	12	(63%)
3. in 20 months from beginning of series	16	(62%)	17	(90%)
Status 20 months from beginning of series:				
1. dead	4	(15%)	0	(0%)
2. at home; doing well	6	(23%)	13	(68%)
3. in sanatorium; condition good	15	(58%)	6	(32%)
4. in sanatorium; progress poor	1	(4%)	0	(0%)
Number Bronchograms	7		2	
Bronchiectasis		5 (71%)		1 (50%)

with this type of lesion were given streptomycin after the research project was completed in February 1948. The dosage formula in these 16 is more nearly that in use at the present time, namely 15 to 33 mg. per kilogram (7 to 15 mg. per pound) body weight per day daily for four to seven days, then 15 to 22 mg. per kilogram (7 to 10 mg. per pound) per day three times a week for a total of 42 days over a period of about three months.

All of these 35 children are alive: 27 of them have gone home and the remaining eight are asymptomatic and making satisfactory progress. None has become deaf and only one has vestibular damage. This child was five months old, had an associated questionable miliary tuberculosis and received 41 mg. per kilogram per day for 61 days. Two children had occasional circumoral paresthesia and two transient joint stiffness.

Our impression of these 35 streptomycin treated children in comparison with the 26 admitted in 1941 may be summed up as follows: 1) the rate of clearing of the parenchymal lesions was bettered by 15 per cent in three months and by 30 per cent in 20 months, 2) the rate of recession of the tracheobronchial lymph nodes was not influenced appreciably, 3) spread to other parts of the lung or body was eliminated, 4) the mortality rate was reduced to zero during this 23 months period, 5) the incidence of bronchiectasis may be reduced but a longer follow-up will be necessary to demonstrate the incidence, 6) streptomycin in our present dosage formula is not likely to cause vestibular damage or to preclude a therapeutic response to a second course should it be needed later, 7) sputum conversion occurred more promptly with streptomycin, 8) endobronchial lesions cleared much more rapidly with streptomycin but the effect on narrowing due to pressure of enlarged tracheobronchial lymph nodes was not remarkable.

Reinfection Type Tuberculosis

Four to eight per cent of the children admitted to Maybury Sanatorium have pulmonary lesions which are classified as reinfection type tuberculosis; i.e., there are no active tuberculous nodes at the hila and deposits of calcium are often found. In other instances the child had a known positive tuberculin reaction with a simple primary lesion shown by x-ray a year or so previously. These differ from the extended and complicated primary lesions in which the pulmonary infiltrations are associated with definite hilar adenopathy and are a part of the original process. A differentiation is essential because the method of treatment usually applied in reinfection cases is contraindicated in all primary cases. The x-ray findings in the child with reinfection tuberculosis are almost identical with those in the adult, with cavitation

quite a prominent feature. The symptom picture is also similar. They tend to progress badly without active therapy. Streptomycin in these cases must be used in conjunction with collapse therapy or surgery as part of a carefully planned course of treatment. One must be certain that the streptomycin effect is being sought at the proper time with reference to the success of the collapse because resistant strains of tubercle bacilli emerge in these cases as readily as they do in adults, after which further streptomycin therapy is useless. In the event the patient is a six-year old child with a large cavity one must evaluate the chances of closing that cavity successfully with phrenic paralysis, pneumothorax, pneumoperitoneum, or resection of the diseased lobe or lung, or of temporizing with one or more of those collapse procedures until the patient reaches the age at which permanent collapse by thoracoplasty might be considered, i.e., 16 to 18 years depending on the completeness of bone maturity demonstrated by x-ray.

A few of the lesions encountered in children are such that phrenic paralysis or pneumoperitoneum will suffice but in the advanced cases more extensive collapse or surgery must be used. Pneumothorax has a fairly good possibility of controlling lesions of moderate extent with small cavities; but when the lesions are extensive or the cavities large there is a definite limitation on the effectiveness of this type of collapse. Another limitation is the improbability of pneumothorax providing successful control of the lesion through the critical adolescent period up to thoracoplasty age. In a six-year old child we try first to control the lesion without pneumothorax since even a five-year course of pneumothorax at this time would have burned this bridge when it might be more desperately needed between 11 and 16 years.

Because prolonged treatment must be anticipated in many of these cases the possibility of needing more than the usual course of streptomycin treatment must always be considered. In preparation for a resection the streptomycin should be given intensively for a week before the operation and six to 10 days afterward; i.e., 22 to 66 mg. per kilogram per day in one to three divided doses. In other cases the streptomycin formula is 15 to 33 mg. per kilogram body weight per day, daily for four to seven days and then 15 to 22 mg. per kilogram per day three times a week to a total of 42 doses over a three months period.

Five children, five to 11 years of age, among the 101 streptomycin treated children had collapse measures or pulmonary resection. Two had left pneumonectomy; they became asymptomatic, negative on gastric culture, and have gone home. Both had been in the sanatorium for some time before streptomycin became available and had a shrunken lung, extensive bronchiectasis, and

consistently positive sputum. They received the drug only at the time of operation: 27 and 33 mg. per kilogram per day for less than two weeks. The other three children were treated with collapse measures and two courses of streptomycin. One who had soft non-cavitative bilateral lesions cleared satisfactorily and became negative on gastric cultures with the first course. Had collapse therapy been used at that time relapse probably would not have occurred. However, the disease did reactivate and now with his second course of streptomycin he is receiving pneumoperitoneum and para-aminosalicylic acid (PAS).

A five year old girl was admitted with two large cavities near the chest wall on the left. With streptomycin the cavities became smaller and left phrenic paralysis was performed during the first course. Serial x-rays have continued to show steady improvement. Five and one-half months after admission she was given another course of streptomycin and pneumoperitoneum was added. She has had a recrush of the left phrenic nerve. For almost a year the cavities have not been seen by x-ray and except for one time the gastric cultures have been negative for tubercle bacilli. Bed rest (modified by the child) is still in effect. Equilibrium and hearing are normal. The fifth case was a small, seven-year old child who had soft exudative lesions throughout both lungs and a 5 cm. cavity with a fluid level in the right antero-lateral segment. With streptomycin the cavity immediately became smaller and right phrenic paralysis and then pneumoperitoneum were added with the result that three months after admission the cavity was invisible by x-ray but gastric cultures did not convert. Three months later coincident with the earliest return of right phrenic nerve function and while the hemi-diaphragm was still markedly elevated the cavity reopened. The second course of streptomycin was started and right pneumothorax attempted. This was abandoned because of adhesions and she was then transferred to the surgical unit for resection.

Nine consecutive reinfection cases were treated in the 1941 series before streptomycin was available with four deaths and five recoveries.

The final results of streptomycin therapy are not yet known but it is expected that at least part of the good early results may be continued so that a greater proportion of these unfortunate children may recover.

Extrapulmonary Tuberculosis

In the extrapulmonary group there are included 13 bone and joint, two lymph adenitis with sinus, one kidney, two pleuritis, one pericarditis, and two peritonitis cases.

The bone and joint cases were given the usual immobilization treatment with surgery as indicated. Streptomycin therapy was not so intensive as in some of the other groups but was continued for longer periods because the bone response is slow. The early cases were treated with the following dosage formula: 15 to 33 mg. per kilogram body weight per day for 42 days, given in one or more daily injections. At present the formula is 15 to 33 mg. per kilogram per day daily for four to seven days then three times a week to a total of 42 doses over a period of three months in the mild cases with no bone destruction and in cases which show prompt disappearance of signs and symptoms. In destructive bone lesions it is given three times a week for 84 doses over a period of about six months. All accessible accumulations of pus are evacuated and when possible, as in the case of a tuberculous rib, the diseased tissue is excised. In cases of empyema 22 mg. per kilogram of body weight is instilled intrapleurally after each aspiration; under intramuscular streptomycin therapy decortication may be carried out. At the time of operation for any extrapulmonary condition 33 mg. of streptomycin per kilogram of body weight is left in the site of operation.

All of these children are alive and all show definite improvement in the lesions. Eight of the 21 children have gone home and the ones in the sanatorium are in good condition. Five had surgery as follows: one fusion of the spine and removal of a portion of tuberculous rib, one fusion of the hip, one decortication for empyema, one nephrectomy, and one pericardial resection. Other bone and joint cases are continuing on immobilization until they are old enough for fusion. Four children had two courses of streptomycin with good results each time.

Because this is a small series it has not been possible to compare streptomycin treated cases with parallel cases treated without it but several observations have been made: 1) general and local improvement is more prompt; 2) there is a decreased tendency to abscess formation and abscesses already present seem to disappear more readily; 3) the bone changes reach the regenerative stage earlier; 4) streptomycin must not be considered as a substitute for any recognized form of therapy but merely as an adjunct to it; 5) the long term results are not yet known.

Discussion

Streptomycin has a rather wide range of use in treating tuberculosis in children. It is mandatory in the treatment of meningitis and miliary tuberculosis. Its next most important use is in the early treatment of tuberculous spreads. Diligence in the detection of new lesions at the earliest possible time cannot be overemph-

asized. It is indicated in acute pulmonary lesions except in simple primary cases and is used effectively in most extrapulmonary tuberculosis. It has a place in the pre- and post-surgical programs. The effect from its use at Maybury Sanatorium has generally been good as shown in Table 2.

The death rate at Maybury Sanatorium has been reduced from 9.8 per cent for a six-year period and 15 per cent for a 26-month period without streptomycin to one per cent for the first 26-month period during which we have had streptomycin. The deaths in meningeal tuberculosis were reduced from 100 per cent to 11 per cent in this same period. This reduction in mortality is no doubt due to the fact that treatment was started early and would have been less dramatic had it been used in the more progressed type of case. Deaths in miliary tuberculosis were reduced from 74 per cent for a six-year period and 88 per cent for a 26-month period without streptomycin to 6 per cent for the 26-month period with

TABLE 2

MORTALITY IN SANATORIUM CHILDREN

	Number	Death	Per cent
Prior to Streptomycin			
Six Years: 1-1-41 to 12-31-46			
Follow-up to 3-1-47			
All Cases	780	77	9.8
Miliary	26	13	50
Miliary-meningitis	24	24	100
Meningitis	15	15	100
24 Months: Comparison Period, 3-44 to 3-46			
Follow-up (2 months) to 3-31-49			
All Cases	200	30	15
Miliary	10	8	80
Miliary-meningitis	7	7	100
Meningitis	3	3	100
During Streptomycin			
21 Months: 4-22-47 to 1-31-49			
Follow-up (3½months) to 6-16-49			
All Cases	281	2	0.7
101 Streptomycin Treated Cases			
Miliary	12	0	0
Miliary-meningitis	4	1	25
Meningitis	5	0	0
Other Cases	80	0	0

streptomycin. The fact that only one death has yet occurred among the streptomycin treated children is interpreted as meaning that life has been preserved but not necessarily that death has been prevented; it may occur later as the result of tuberculosis. Streptomycin does not prevent the development of new tuberculous lesions or spreads nor does it give complete assurance against the reactivation of already treated lesions. Evidence has recently been presented to show that the addition of promizole to streptomycin therapy will prevent the development of meningitis in miliary tuberculosis cases, will reduce the incidence of neurological sequelae and will reduce the proportion of relapses.[8] Streptomycin becomes less potent in proportion to the age of the lesions and is almost ineffective against caseous lesions. It cannot compensate for the lack of other good treatment but merely supplements it. The adequate drainage of all abscess pockets is necessary to a good streptomycin effect. Streptomycin is a toxic substance and must be used cautiously.

Children tend to tolerate large doses of streptomycin relatively better than adults but they do demonstrate acute toxic and neurotoxic manifestations. When streptomycin is to be used as a life saving treatment it must be given in whatever dosage is necessary despite the risks of loss of equilibrium. In other cases the dosage should be held below 35 mg. per kilogram body weight per day. Children do learn to compensate for the loss of equilibrium but it is not reasonable to subject them to this disability if safe dosage will provide a suitable therapeutic result.

TABLE 3

TOXIC REACTIONS AMONG 101 CHILDREN RECEIVING STREPTOMYCIN

	No.	Hearing Lost	Caloric Test Positive
Meningitis	9	1	9
Predominantly pulmonary (exclusive of PBC)	36		
1. Miliary	12	0	9
2. ? miliary	6	0	4
3. Babies 2-6 months	5	0	4
4. Others	13	0	0
Primary with bronchial complication (PBC)	35		
1. Trudeau series	19	0	1
2. Others	16	0	0
Predominantly extrapulmonary (exclusive of meningitis)	21	0	0

Intensive therapy for longer than 28 days carries the possibility of streptomycin resistant tubercle bacilli emerging and curtailing further therapeutic value of the drug. For this reason initial periods of intensive treatment must be well limited except in those cases in which the clinical effect is delayed and prolonged high dosage is indicated.

The dosage formula given for each group of cases reported is the result of modifying the various early dosage schedules and arriving at one which experience had shown to be suitable. These formulae may be changed in the future based upon further observations but at the present they are the ones being used at Maybury Sanatorium. They are therapeutically sound and are recommended for use by others in treating cases similar to those reported above. Dihydro-streptomycin is reportedly[9] less toxic than the earlier preparations used in this study and may permit the use of more intensive therapy without the hazards of toxic manifestations. The emergence of resistant organisms is apparently as likely with dihydro-streptomycin as with the regular variety. Combined treatment with other chemotherapeutic agents may also modify the dosage schedules and the results. The results of streptomycin therapy have ranged from dramatic recoveries from tuberculous meningitis to disappointing failures in caseating glands but generally they were good. Many children are alive and well because they were treated with streptomycin, many others are recovering. It is anticipated that further good results will be recorded in the future.

Comment

From April 1947 through January 1949, 101 children at Maybury Sanatorium were treated with streptomycin and the results compared with a similar series treated previously in an identical manner without streptomycin. The 101 children included miliary and meningeal cases, severe primary, primary with bronchial complications, reinfection and extrapulmonary cases. The miliary and meningitis cases were given intensive streptomycin therapy at the earliest possible time after the onset of symptoms. The formula for intramuscular therapy was 55 to 88 mg. per kilogram of body weight per day for three to six months depending upon the effect and then 25 to 44 mg. per kilogram per day for the balance of six months. The daily amount was divided into two or three doses according to the size of the child. The meningitis cases were also given intrathecal streptomycin according to the following formula: 2.5 mg. per kilogram, up to 50 mg. maximum, daily for three weeks, then the same dose three times per week for three months and then one-half that dose twice weekly for the balance of six months.

The same courses were repeated in case of relapse. Eighteen cases of miliary tuberculosis, nine of meningitis, and four of miliary-meningitis were so treated. All miliary and meningitis cases and three of the miliary-meningitis cases survived and were apparently recovered at the end of the survey, May 1, 1949. One miliary-meningitis case expired in relapse after making satisfactory early improvement. All had vestibular damage, all compensated well, one is deaf. In the previously treated comparison series, 100 per cent meningitis and 80 per cent miliary cases had died.

Streptomycin was given to five babies with severe primary tuberculosis using the formula of 33 to 66 mg. per kilogram body weight for four to seven days and then one-half that dose three times per week for the balance of 42 doses with satisfactory results. Three recovered completely and two were still making good progress in the sanatorium at the end of the study period.

Nearly 20 per cent of the children admitted to the sanatorium were of the primary with bronchial complication type (extensive epituberculosis). In the previously treated comparison series, 15 per cent had died in the two-year and 28 per cent in a ten-year follow-up study. Bronchial obstruction of various types was found in 74 per cent of the cases. Seventy per cent of them were later found to have bronchiectasis in the involved area. Thirty-five children with this type of tuberculosis were given streptomycin using the following formula: 15 to 33 mg. per kilogram daily for four to seven days, then 15 to 22 mg. per kilogram three times a week for a total of 42 doses over a period of about three months. All 35 children survived and apparently recovered. None suffered any demonstrable vestibular damage. In comparison with the series treated in 1941, the results were as follows: the rate of resolution in the parenchymal lesions were bettered by 15 per cent in three months and by 30 per cent in 20 months, the rate of recession in the tracheo-bronchial nodes was not appreciably changed, spreads to other parts of body, prevalent in the comparison series, was eliminated completely, the mortality was reduced to zero over a 23-month study period and it is anticipated that future studies will show a marked reduction in the incidence of bronchiectasis. Sputum conversions occurred more promptly and endobronchial lesions cleared much more rapidly.

About six per cent of the children admitted by Maybury Sanatorium have reinfection type pulmonary tuberculosis. Five such cases, ranging in age from five to eleven years were included in the 101 cases treated with streptomycin. Besides streptomycin using the same formula as above these children were given collapse or surgical therapy. All five children have survived and all but one give promise of recovery. In the 1941 series four out of

nine children expired within two years. In the extrapulmonary group were included 13 bone and joint, two adenitis with sinus, two pleuritis, two peritonitis, one pericarditis, and one renal tuberculosis cases. In addition to streptomycin each child received all other indicated therapy. The streptomycin dosage formula was 15 to 33 mg. kilogram daily for four to seven days and then three days per week for a total of 42 or 84 dose-days depending upon the response. In the empyema cases, 22 mg. per kilogram were instilled into the pleural space following aspirations. All 21 children survived and made better than previously observed progress.

The overall results of streptomycin therapy in 101 children, observed over a period of 23 months was good. The death rate was reduced from 15 per cent for a comparable 26 month period to 1 per cent. Only one death occurred in the 101 cases treated. A good chance of recovery is given every child with tuberculosis, even miliary and meningitis cases if adequate treatment can be started early and continued for six months or more.

SUMMARY

The results of treating 101 cases of tuberculosis in children with streptomycin in comparison with previously treated cases is reported. The treatment programs used in five different types of cases are outlined including the recommended streptomycin dosage formulae. The results of therapy in each group of cases is recorded with comparative death rates. The unfavorable effects of streptomycin and the precautionary methods are discussed as well as therapeutic limitations.

RESUMEN

Se refieren los resultados del tratamiento de 101 niños con tuberculosis por medio de la estreptomicina, en comparación con casos tratados anteriormente. Los planes de tratamiento usados en cinco tipos de casos diferentes se describen, incluyendo las dosificaciones de estreptomicina recomendadas.

Los resultados del tratamiento en cada grupo son presentados con los coeficientes de mortalidad comparativamente.

También se presentan los resultados desfavorables y se discuten las precauciones así como las limitaciones terapéuticas.

REFERENCES

1 Thompson, J. L. Jr. and Wagenheim, H. H.: "The Use of Streptomycin in Acute Miliary Tuberculosis: Report of a Case," *M. Ann. District of Columbia*, 15:265, 1946.
2 Cooke, R. E., Dunphy, D. L. and Blake, F. G.: "Streptomycin in Tuberculous Meningitis: A Report of Its Use in a One Year Old Infant," *Yale J. Biol. and Med.*, 18:221, 1946.
3 Lincoln, E. M., Kirmse, T. W. and DeVito, E.: "Tuberculous Meningitis," *J.A.M.A.*, 136:593, 1946.

4 Morgan, H. J., Hunt, J. S., Kent, L. R. and Carlisle, M. J.: *Vanderbilt Univ. and Merk & Co. Exhibit,* New Jersey State Medical Society, April, 1947.
5 Levinson, Abraham: "Streptomycin Therapy in Tuberculous Meningitis," *Am. J. Dis. of Children,* 77:709, 1949.
6 Jones, E. M., Peck, W. M. and Willis, H. S.: "Bronchiectasis Following Primary Tuberculosis," *Am. J. Dis. of Children,* 72:296, 1946.
7 Jones, E. M., Rafferty, T. N. and Willis, H. S.: "Primary Tuberculosis Complicated by Bronchial Tuberculosis with Atelectasis," *Am. Rev. Tuberc.,* 46:392, 1942.
8 Lincoln, E. M. and Kirmse, T. W.: "Streptomycin and Promizole in Miliary Tuberculosis and Tuberculous Meningitis in Children," *The Lancet,* 767, May 7, 1949.

Streptomycin Dosage in the Treatment of Tuberculosis

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The efficacy of streptomycin in the treatment of many forms of clinical tuberculosis has been established. The early successes with this measure were achieved with the use of two grams or more, given daily in divided doses, over a period of many months. With this regimen, loss of vestibular function, complete and permanent, was to be expected. Renal irritation with a few cases of serious and even fatal renal damage, a high incidence of allergic manifestations, chiefly dermatologic, pain and induration at the site of injection, facial paresthesias and other toxic effects were also observed. In view of the severity of the disease for which streptomycin was being administered in most cases and the importance of getting the maximum therapeutic response from any agent given in conditions with such poor prognosis, the toxic consequences of large doses of streptomycin were accepted as necessary concomitants of the treatment. These ill effects, together with high cost and restricted supply of streptomycin limited the use of this agent to those patients with the most urgent indications and adequate financial resources.

Streptomycin usually causes a decrease of fever and of tachycardia, cough, sputum volume and bacillary content. These effects are most marked in the early weeks or months of treatment. Complete healing, with disappearance of all abnormal densities on x-ray, cavity closure, sputum conversion and arrest of tuberculosis, as a result of streptomycin treatment alone has been, unfortunately, an uncommon experience. More often the streptomycin has merely diminished the acute inflammatory exudate in the lungs and prepared, or assisted, the patient to profit from further collapse measures, or has resulted in subsidence of complications such as laryngeal or tracheobronchial ulceration, intestinal tuberculosis, draining sinuses, etc.

If pulmonary lesions remain active such complications are apt to recur or develop anew at a later date. Recurrences do not appear to be prevented by prolongation of the original course of treatment. Accordingly, it has been recommended that streptomycin be given in courses of six weeks or less at a time, instead of the

*From the Western Trudeau Streptomycin Laboratory, Olive View, California, aided by Research Grants 541 and 1104, United States Public Health Service.

original recommendations of three or more months continuously. Such short courses may give results little inferior to those of the longer courses and leave the patient with organisms still susceptible to streptomycin.

Animal experiments showed that large doses and frequent administration to maintain continuously high blood levels of streptomycin were not necessary for optimal therapeutic effects. Extensive clinical experiences demonstrated that 1.0 gram doses given in one or two injections daily, yielded clinical therapeutic effects indistinguishable from those obtained with the larger doses and more frequent administrations, with marked decrease in the incidence and severity of toxic manifestations. Further reduction in dosage to 0.5 gram in one injection daily revealed similar effectiveness, with absence of vestibular and visceral toxicity. With the lowering in cost, and increase in availability of streptomycin, this elimination of most of its ill effects greatly extended the indications for its use in the treatment of tuberculous lesions.

Clinical and laboratory investigations at the Olive View Sanatorium have demonstrated the lower limits of therapeutically effective dosage. Amounts of 0.1 gram or less, given daily, were found to be insufficient, producing little of the symptomatic or objective improvement generally observed with larger doses of streptomycin. Administration of 0.2 gram per day gave evidence of therapeutic effect in the majority of patients so treated but failed in a small number who later responded to still larger doses.

If streptomycin is to be given daily, doses of 0.33 gram are well tolerated, and adequate, above the minimal effective dose, with practically no toxicity. If it is given at greater intervals it becomes important to know how large a dose may be given at a single time and what is the least amount which might be effective, and to determine what intervals may be designated.

Although as much as 10.0 grams of streptomycin have been given over a 24 hour period, this might be fatal if administered in a single dose. Single intramuscular injection of 3.0 grams at one time have been given repeatedly without serious consequences. However, doses of 3.0 grams or even 2.0 grams given at one injection are usually associated with marked parathesias and other transitory nervous disturbances. Although patients may tolerate such sensory disturbances, if forewarned and assured of their harmlessness, it may be better to use doses devoid of even such causes of alarm.

Doses of 1.0 gram given once a week produced a definite therapeutic response in many patients, but failed in some others who later improved when given larger amounts. Doses of 2.0 or 3.0 grams, however, appeared to be just as effective as larger doses.

Intermittent regimens of 1.0 gram every three days or 2.0 grams once a week are now being followed in many institutions. Dihydrostreptomycin has also been given in these dose schedules with similar response.

The increased intervals are used chiefly in the hope that by this means the development of resistant forms of tubercle bacilli which are refractory to streptomycin may be delayed. The limited data so far available, suggests that administration of streptomycin at intervals several days apart, or in repeated short daily courses with intervening rest periods, results in a prolongation of the total elapsed time before resistant forms appear.

It is not necessary to give large toxic doses of streptomycin in the treatment of pulmonary tuberculosis and its complications. Doses of 0.33 gram of streptomycin daily, 1.0 gram administered every three days, or 2.0 grams once a week are usually safe and effective. If symptomatic response is not observed within two weeks following the starting of such dosage, or if relapse occurs after initial improvement during continuation of treatment, the dose may be increased but treatment should not be continued if the lack of beneficial effect is due to the development of streptomycin-resistant bacilli.

Combinations of streptomycin with other bacteriostatic agents not only yield enhanced therapeutic effect, but result in a delay in the development of resistant forms. Although the sulfones have proved effective in experimental animals and produce response in some patients, they are too toxic for general recommendation. Para-aminosalicylic acid (PAS) is now available in this country and has proved both experimentally and clinically to have effect similar to that of streptomycin though perhaps somewhat less. It is, moreover, effective in instances of infection with streptomycin-resistant organisms.

Three grams of para-aminosalicylic acid with 1½ grams of sodium bicarbonate and 1½ grams of sugar, freshly dissolved in a glass of water, may be given four times a day. The PAS should be given at the same time as the streptomycin rather than at an earlier or later time in order to have the best effect on delay in the development of resistant forms. It may be possible, by giving PAS only a few days a week, coincident with the streptomycin, to obtain this beneficial synergistic effect while still avoiding much of the gastrointestinal toxicity which accompanies many of the present-day preparations of PAS. Treatment with PAS on the day of an intramuscular injection of streptomycin and on the following day only may be sufficient to secure this synergistic effect.

Careful selection of the optimal time for administration, giving the streptomycin intermittently with several days to a week inter-

val between doses, and combining streptomycin with para-aminosalicylic acid or other chemotherapeutic agent, and giving courses only long enough to obtain the desired result, will delay the development of resistant forms. It may be possible to secure the benefit of repeated courses of streptomycin chemotherapy as indications arise in the same patients before the development of streptomycin-resistant organisms renders such treatment futile. The indications for this treatment have been considerably extended and the objections to it greatly diminished by these measures so that the majority of patients suffering from active tuberculosis may now be considered potential candidates for modern chemotherapeutic measures.

SUMMARY

Streptomycin need not be administered in large amounts, four to eight daily doses, totalling 1 to 3 grams a day for three to six months, to elicit a favorable response in the treatment of tuberculosis. Such a frequent, heavy and prolonged regimen is likely to injure the patient and leads to the emergence of resistant organisms which render further use of this agent futile.

The minimal effective dose is about 0.2 grams a day, or 4 milligrams per Kg., and double this amount offers an adequate factor of safety. Two grams of streptomycin given only once a week or 1 gram twice a week, is not only less toxic, but is less rapidly followed by the development of resistant bacilli. Combinations of streptomycin with collapse therapy and with para-aminosalicylic acid, or other chemotherapeutic agents, still further conserve its efficacy and extend the indications for its use.

RESUMEN

Para producir una respuesta favorable en el tratamiento de la tuberculosis por la estreptomicina, no se necesita que ésta sea administrada en grandes cantidades a las dosis de cuatro a ocho dosis diarias con un total de 1 a 3 gramos.

Tales dosis frecuentes y grandes son capaces de dañar al enfermo y conducir a la aparición de organismos resistentes y hacer su uso ineficaz.

La dosis mínima eficaz es alrededor de 0.2 por día o 4 miligramos por kilo de peso y el doble de esto proporciona un factor adecuado de seguridad.

Dos gramos de estreptomicina dados solamente una vez por semana es una dosis no solo menos tóxica sino menos rápidamente seguida por desarrollo de resistencia bacteriana. Las combinaciones de estreptomicina con colapsoterapia y con ácido para-aminosalicílico aún sirven para conservar su eficacia y para ampliar las indicaciones para su uso.

Streptomycin in the Treatment of Miliary and Meningeal Tuberculosis Based on a Study of 30 Cases*

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Introduction

Whether acute hematogenous dissemination of tubercle bacilli results in miliary tuberculosis, tuberculous meningitis, or a combination of the two, the ensuing diseases, though very closely related etiologically, are nevertheless distinct clinical entities, each with a different prognosis and therapy.

The immediate mechanism, which is responsible for the infection assuming one or the other clinical form, is a matter of speculation and may be due to a variety of causes such as: the anatomical position of the primary source of dissemination, the amount of infected material thrown into the circulation, the frequency of disseminations, possibly the vaguely understood individual variation in organ susceptibility, the patients' general resistance, or a combination of these and other causes. An answer to this question, which may supply the key to prevention and, perhaps, to more successful therapy, must await further study.

The reported results of treatment of acute disseminated tuberculosis with streptomycin have varied greatly. Only certain types of miliary disease (probably of a predominant local pulmonary type) have responded with any degree of permanent success.

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Reports of successful treatment in this type of disease vary roughly between 40 and 100 per cent. Uncomplicated meningitis has been reported as responding favorably in 20 to 75 per cent of cases, while combined miliary and meningeal disease has shown a variation from 5.5 to 58.5 per cent favorable results, depending chiefly on the time during which observation has been continued after treatment. If every case were followed for two to three years, the percentage of survivors would probably be reduced to half or less of the first reports. The degree of recovery has varied from a mere prolongation of life, to the production of various types of neurological "cripples," or to a temporary (or permanent) return to normal health. In general, the reported success has depended (besides the variation in types of disease mentioned) upon the age of the patient; the duration of the disease before the treatment was begun; possibly to a certain extent upon the method of treatment, and most important of all, upon the *length of time the patient was observed after the treatment was finished.*

Some of the more important studies will be reviewed. There are numerous single case reports of survivals, observed from several months to two years, including those of Cooke, Dumphy, and Blake,[1] Applebaum and Halkin,[2] Mehas and Truax,[3] Bauer and Sauer,[4] and many others. Such reports are, however, of limited value. Larger groups of cases, with longer periods of observation after treatment, are necessary to permit any reliable conclusions.

Among the first hundred cases of all forms of tuberculosis treated by Hinshaw and his associates,[5] 12 had miliary tuberculosis and/or meningitis. Five of these were alive at the time the report was made, but only three (25 per cent) have survived for three years.[6]

Cocchi and Pasquinucci[7] reported in April 1947 on 28 cases of meningitis, for the most part in children, which had been treated between December 11, 1946 and April 11, 1947; 21 cases (73 per cent) survived. Obviously the time limit was too short for a worthwhile appraisal of results.

Debré, Thieffry, and Brissaud[8,9] reported 43 survivors (46 per cent) amongst 93 cases of meningitis in children treated between September and December 1, 1947. Only 27 (29.1 per cent) of the cases, however, were in good condition and only 7 (8 per cent) entirely well at the time of their second report. The cases of acute miliary tuberculosis were especially noteworthy. Of 10 such cases, free from meningitis, eight were living (80 per cent); of 15 who had meningitis at the time treatment was begun, six were living (40 per cent); and of six with meningitis which developed *after* treatment was begun only one was alive (16.7 per cent). Debré, Brissaud, and Noufflard[10] added seven more cases to the series

(making 100 cases in all) with 46 cases (46 per cent) regarded as "cured" two to 10 months after treatment was finished.

Decourt and his associates[11] treated 72 cases of meningitis during more than a year, at the end of which time only 13.9 per cent had sufficiently recovered so that treatment could be stopped; 33.3 per cent were still under treatment; 22.2 per cent who died had their lives prolonged for varying periods of time, and 30.5 per cent died without revealing any effect of the drug. He stated significantly that in no case could they describe any patient as *cured*.

Fouquet[12] treated 50 cases of "pure" (simple) meningitis and reported nine (18 per cent) were clinically "cured"; eight (16 per cent) were in "good condition"; thirteen (26 per cent) were still under treatment; four (8 per cent) had developed "chronic meningitis," and sixteen (32 per cent) were dead.

De Lavergne[13] stated that "favorable" results could be expected in about 25 to 30 per cent of patients with tuberculous meningitis. Mouriquand[14] reported that 24 (58.5 per cent) cases of "pure" meningitis were living out of 41 treated cases; and only one of four (25 per cent) patients with combined miliary-meningeal tuberculosis had survived.

Cathala and Bastin,[15] in 41 cases of "pure" meningitis in children, reported that 17 (41.5 per cent) were living and 24 were dead. Of the living, 12 were still under treatment; among the five whose treatment was completed, only two were well. Of 21 cases of miliary tuberculosis, eight were dead, eight were still under treatment, and five had completed treatment; of the latter, only two were entirely well. Of 16 miliary-meningitis patients, seven (43.7 per cent) were living at the time of the report, four of whom were still under treatment and three in grave condition.

Sédallian and his associates[16] reported that of 35 adult cases of miliary disease only six (17.1 per cent) were living. Etienne Bernard[17] reported 20 (25.9 per cent) of 78 adult cases of meningitis to have survived at least eight months. In a later report by the same author,[18] only 14 of the same cases (18 per cent) were alive after 14 months.

Van Goidsenhoven, Stevens and Crolla[19] reported 21 (65.6 per cent) of 32 cases with generalized disease to be alive five to 12 months after treatment was started. Among other things they warn, that in spite of immediate improvement in a majority of cases, there should be the "greatest reserve" in making an ultimate prognosis for "at least a year after cessation of treatment."

Marshall and his associates[20] treated 105 cases of tuberculous meningitis in children; 30 of them (28 per cent) survived for a period of 120 days or more. In general, the younger the children and the longer the disease had existed before treatment, the worse

were the results. The work of these authors also seemed to indicate that the addition of some intrathecal medication was advantageous because of 72 cases receiving combined intramuscular and intrathecal administration, 25 (35 per cent) survived whereas only three (11 per cent) of 28 cases who received intramuscular treatment alone survived.

Loffler and Piotti[21] observed 13 cases of meningitis in adults for about a year; three (23 per cent) survived. Life was believed to have been prolonged (in one instance for 328 days) in all fatal cases.

Lincoln, Kirmse and De Vito[22] treated seven cases of meningitis. Six (85 per cent) survived for from two to eight months and only two had post-treatment complications.

Since most of the European reports were on children, the report of Bunn[23] from the Veterans Administration Hospitals has given the best available data on adults, and the cases have been followed longer than any others of which records are available to us. Out of 100 cases of miliary tuberculosis and/or meningitis, 24 (24 per cent) were alive 11 to 25 months after treatment was completed and 15 (15 per cent) were entirely well. Twelve (58.2 per cent) of 22 miliary cases, nine (20.9 per cent) of 43 cases of simple meningitis, and only three (8.5 per cent) of 35 cases of miliary-meningitis, were alive at the time the report was made.

The dosage which has been used in the treatment of generalized disease has been quite variable. With the exception of Van Goidsenhoven, who gave intrathecal treatment prophylactically, no intrathecal treatment was given if the miliary tuberculosis occurred without meningitis. Most investigators who have compared combined intrathecal and intramuscular therapy with intramuscular alone in the treatment of meningitis, have been unalterably in favor of the former regimen.

It would require much discussion to outline the various regimens which have been used. In general, they may be divided into large, medium, and small dosages, both intrathecally and intramuscularly, and in many instances each category has been supplemented with adjuvant drugs, such as the sulphones, vitamins A, B, and D, and with surgery.[10,24]

The duration of intramuscular treatment has varied from three to eight months. Intrathecal injections have been given with varying frequency (daily to weekly) over various periods of time, and interrupted courses (one week on and two weeks off) have been used. Some authors varied the treatment with practically every patient.

The intramuscular dosage varied from a total of 2 gm. a day down to 0.1 gm. a day and has usually been given in six to eight

equally divided doses. The intrathecal dosage ranged from 0.1 to 0.2 gm. to as low as 0.015 gm. a day. Recently, there has been a tendency to use smaller dosage and, especially, fewer and more widely spaced intrathecal injections.

Analysis of Clinical Material and Results of Treatment

From January 1, 1947 to April 15, 1949, 1212 patients, all adult males, were treated on the Tuberculosis Service of this hospital. Thirty of these patients were either admitted for, or have subsequently developed, one or another form of the miliary-meningeal group of diseases.

The present report is based on a study of these 30 cases. They are divisible as follows: Nine cases of miliary tuberculosis, 14 of tuberculous meningitis, and seven of tuberculous meningitis superimposed on miliary tuberculosis (Table 1).

Treatment Regimens:

Miliary Tuberculosis: The first two patients were treated with 1 gm. of streptomycin intramuscularly for 111 and 120 days respectively and the third, a terminal case, received 2 gm. daily and survived only seven days. Subsequent to this, all patients with miliary tuberculosis were placed on a regimen of 1 gm. of streptomycin intramuscularly, with the addition of 4 gm. of promin intravenously, daily, for 120 days. Promin was omitted every third week of therapy. When meningitis was recognized in a patient under treatment for miliary tuberculosis, his treatment was changed to the combined miliary-meningeal regimen (see below).

Tuberculous Meningitis: The first four patients were placed on a regimen of 1.8 to 2 gm. of streptomycin intramuscularly, daily, and 0.05 gm. of streptomycin intraspinally three times per week for 120 days. The remaining 10 patients were placed on a regimen of 2 gm. of streptomycin intramuscularly and 4 gm. of promin intravenously, daily, and 0.05 gm. of streptomycin intraspinally

TABLE 1

Results in All Types of Miliary and Meningeal Tuberculosis

	Died During RX	Died After RX	Survived to Present	Total
Miliary alone	3*	0	6 (66.7%)	9
Meningitis alone	7	4	3 (21.4%)	14
Miliary-meningitis	6	0	1 (14.3%)	7
TOTAL	16	4	10 (33.3%)	30

*Terminal state on admission.

three times per week, for 120 days. Promin was omitted every third week of therapy. Intraspinal therapy was omitted in four patients (7, 8, 12 and 14).

Combined Miliary-Meningeal Tuberculosis: The seven patients in this group received treatment similar to those with meningitis alone, except that intramuscular streptomycin was increased to 4 gm. per day for the first two weeks and then reduced to 3 gm. per day for the remainder of the treatment period.

Miliary Tuberculosis:

During the period covered by this report, nine patients received streptomycin therapy for miliary tuberculosis alone (Table 2). Their ages ranged from 22 to 54 years. Eight of the nine patients were Negroes. Taking into consideration the usual proportion of Negro to white patients on our wards, the incidence of miliary tuberculosis was about 28 times greater in the Negro than in the white patients.

The estimated duration of symptoms suggestive of miliary tuberculosis before treatment was started, ranged from one to 18 weeks. The vast majority of patients were acutely ill and their temperatures ranged from 101 to 104 degrees F. Shortness of breath was a common complaint. Comparable roentgenograms were not available in three patients (Table 2) who were in terminal state and died on the 7th, 10th and 37th day of therapy respectively and

TABLE 2

Miliary Tuberculosis — Treated Before April 15, 1949

Case No.	Name	Age	Race	Sympt. Pre-RX (Wks.)	Duration of RX (Days)	X-Ray Changes 1st Noted (Wks.)	X-Ray Changes Degree of Improv.	STATUS, 4-15-49 Living (Days*)	STATUS, 4-15-49 Dead (Days*)
1	R.S.	27	C	16	111	6	Mkd.	111**	
2	R.J.	51	C	1	120	12	Mod.	524	
3	W.H.	22	C	4	7				7
4	N.L.	23	W	4	120	8	Mkd.	453	
5	R.B.	42	C	2	37				37
6	J.B.	54	C	2	120	8	Mkd.	365	
7	T.W.	38	C	1	10				10
8	J.M.	34	C	18	120	4	Clear	358	
9	H.M.	31	C	16	120	4	Mkd.	191	

*Days after first starting treatment for miliary tuberculosis.

**AWOL on the 111th day and lost to study. Reported to be alive April 30, 1949.

could not be x-rayed. In the remaining six patients, the roentgenograms revealed marked to complete clearing in five patients and moderate clearing in one. Improvement was often noted six weeks after starting treatment and was observed on all two-month films, but continued through and following the treatment period of 120 days. One patient left the hospital of his own accord twice during the height of his illness and returned, and though his miliary dissemination showed moderate clearing he developed progressive pulmonary tuberculosis and his prognosis is poor.

TABLE 3

Tuberculous Meningitis — Treated Before April 15, 1949

Case No.	Name	Age	Race	Duration Sympt. Pre-RX (Wks.)	Assoc. Tb. Cond.	Duration of RX (Days)	STATUS, 4-15-49 Living (Days[1])	Dead (Days[1])
1	W.L.	58	C	0.5	Pul.	63		63
2	E.F.	23	W	12	Pul.	120		259
3	W.K.	29	W	1.5	Ankle	120 62[2] 75[2]		354
4	J.A.	54	W	4.5	Pul.	120[3] 42[3]		188
5	J.M.	29	C	2	Adeni-tis	66		164
6	F.McC.	23	W	2	Pul.	120	426	
7	P.T.	30	W	2	Pul. Empy.	98		151
8	F.M.	38	W	1.5	Pul.	120		161
9	W.W.	50	C	4	Pul.	10		10
10	E.J.	53	C	2		28		28
11	J.M.J.	29	W	1	Pl. Effus.	7		7
12	J.C.	29	W	2	Adeni-tis	180[4]	180	
13	L.V.W.	56	C	2	Pul. Larynx	1		1
14	W.O.D.	19	C	6	Adeni-tis	120	177	

[1]Days after first starting streptomycin treatment for tuberculous meningitis.

[2]Relapsed one month after first course; retreated with streptomycin plus promin for 62 days, improved; relapsed again three weeks later, retreated 75 days without benefit and died.

[3]Relapsed three weeks after first course and retreated with streptomycin plus promin for 42 days.

[4]Treated an extra two months.

Tuberculous Meningitis:

During the period under discussion 14 patients had tuberculous meningitis, without miliary tuberculosis, and all were treated with streptomycin (Table 3). Their ages ranged from 19 to 58 years. Six were Negroes and eight were white. The incidence of tuberculous meningitis was about three times greater in the Negro than in the white patients. Five patients (5, 7, 8, 12 and 13) developed meningitis during or shortly after a course of streptomycin for other tuberculous conditions.

Of the 14 patients, 11 died and three survived to the date of this report. Four patients (9, 10, 11 and 13) died between the first and twenty-eighth day of therapy; and were not treated long enough to contribute significant data to Table 4. Three patients (6, 12 and 14) were alive six to 14 months after the beginning of therapy and had no symptoms referable to the central nervous system; although some residual abnormalities of the cerebrospinal fluid persisted (see Table 4 and Case Report 1).

Intraspinal therapy was omitted in four patients and two were alive six months after the start of treatment. Streptomycin was given intraspinally in 10 patients and one was alive 14 months after the start of therapy.

Symptoms: Headache was the earliest symptom suggestive of meningitis and was present in all patients. It was usually intermittent at first, becoming more and more constant as the disease progressed. Symptoms referable to the central nervous system varied in severity from headache through confusion or restlessness to drowsiness, stupor, and coma. Defervescence of fever, for varying periods of time, was noted in all patients.

Symptoms referable to the central nervous system were not improved in the four patients who died on the first, seventh, tenth and twenty-eighth day of therapy. The remaining 10 patients were treated two months or more and all but one (No. 7) showed at least temporary improvement of cerebral symptoms to a moderate or marked degree. This improvement was sustained from three to 14 months in six patients and two relapsed and died 259 and 354 days respectively after the beginning of treatment.

Neurological Findings: Nuchal rigidity was the earliest neurological finding in most cases and this rarely improved for more than a few days. This sign was absent throughout in one patient (No. 6). Kernig, Brudzinski, and/or Babinski reflexes were observed intermittently in 11 of the 14 cases. Absence of abdominal or cremasteric reflexes were noted in nine cases.

Of the 10 patients treated more than 28 days nine developed various paralyses with only one (No. 12) surviving to date; and

eight developed bladder or bowel incontinence with one survival (No. 14).

Cerebrospinal Fluid (Table 4): Four of the more significant cerebrospinal fluid elements were selected and recorded. Four patients were treated less than 30 days and were therefore omitted from this table since they did not contribute significant data for discussion.

Accepting 150 mm. as the upper limit of normal spinal fluid pressure in the lateral recumbent position, it was elevated in all patients at one time or another before therapy. During treatment, some lowering of pressure was recorded in seven of the 10 patients; it reached zero in one patient (No. 4) and was associated with spinal block, paraplegia, and bladder and bowel incontinence.

The protein content was elevated before treatment in most of the cases. During treatment it increased further in seven of the 10 cases. In several patients it remained extremely high while the cell count was diminishing, the sugar level rising, and the clinical condition improving.

The sugar content was less than 50 mg. in seven instances before treatment. During treatment the sugar level rose in nine and fell again as relapses occurred. On the whole, the sugar content followed closely other evidences of improvement or relapse.

The total cell count was elevated in all cases on at least one examination before treatment. During treatment it fell for some period of time in most cases and was in fair agreement with the clinical course.

Combined Miliary-Meningeal Tuberculosis:

During the period covered by this report, meningitis was diagnosed on the 18th to 80th day of therapy for miliary tuberculosis in six patients. The seventh patient (No. 2) received 0.5 gm. of streptomycin for tuberculous laryngitis for 59 days before tuberculous meningitis and miliary tuberculosis were recognized (Table 5). Their ages ranged from 25 to 63 years. Five patients were Negroes and two were white. The incidence of combined miliary-meningeal tuberculosis in Negro patients was about nine times that in white. Temperatures tended to reach higher levels in this group than in the group with meningitis alone. Temporary response to streptomycin therapy occurred in all but was sustained in only one patient.

Of the seven patients, six died and one survived to date of this report (see Case Report No. 2). Of the six who died, four showed temporary improvement of symptoms referable to the central nervous system. The abnormal neurological findings in this group

TABLE 4 — Cerebrospinal Fluid Findings (Tuberculous Meningitis)

Case No.	Name	Pre-RX		DAYS AFTER START OF STREPTOMYCIN 0-15	15-30	30-60	60-90	90-120	120-180	180-240	240-300	300-360	Diag. Conf. by
1	W.L.	Pres.	300 mm.	215	230	360	Died						S x 6
		Prot.	185 mg.		325								C x 2
		Sugar	33 mg.	41	57								
		Cells	75	84	256	100							
2	E.F.	Pres.	200 mm.	120	90	180		70			Died		S
		Prot.		850	950								
		Sugar	55 mg.	42	59	65		15					
		Cells	207	159	84	19		222					
3	W.K.	Pres.	480 mm.	280	260	200			310	260	440	Died	S x 2
		Prot.	100 mg.	71	165	185		62	58	300	800		C x 6
		Sugar	37 mg.	37.5	15	37		70	40	54	30.5		
		Cells	286	37	14	16		154	700	116	30		
4	J.A.	Pres.	290 mm.	120	85	70		80	0	Died			S x 1
		Prot.	49 mg.		195			350	145				C x 3
		Sugar	30 mg.	55	34	55		25	50.4				
		Cells	200	340	73	23		86	40				P.M.
5	J.M.	Pres.	130 mm.	370	200	370		140	Died				
		Prot.	300 mg.	820	400	800		114					C
		Sugar	30 mg.	69	66	75		47					
		Cells	78	18	14	12		14					P.M.
6	F.McC.*	Pres.	200 mm.	250	250	170		180	160	140	120	140	
		Prot.	492 mg.	355	495	400		594	350	212	121	100	
		Sugar	30 mg.	20	20	41		50	65	63	60	66	G.P.
		Cells	66	296	386	96		228	28		34	2	
7	P.T.	Pres.	200 mm.	265		240		Died					
		Prot.	126 mg.	130	65	92.5	56						
		Sugar	52.3 mg.	43.5	40	31	30						
		Cells	174	1026	30	2							P.M.
8	F.M.	Pres.	330 mm.		205	220	190	70	Died				
		Prot.	140 mg.		325	500		1000					
		Sugar	37.5 mg.		40	45	30	50					
		Cells	412		24	192	18	10					P.M.
9	W.W.	Treated for meningitis from 1 to 28											

8	P.M.	Pres.	660 mm.						Died		
		Prot.	140 mg.	325	500		1000				
		Sugar	37.5 mg.	40	45	30	50				
		Cells	412	24	192	18	10				P.M.
9	W.W.	Treated for meningitis from 1 to 28 days and supplied no significant data for this table.									
10	E.J.										All conf.
11	J.M.J.										
12	J.F.C.	Pres.		600	450	330	130	120	130	Living	
		Prot.	190 mg.	163	360	550	520	440	181		C x 2
		Sugar	54 mg.	72	70	74	65	69	83		G.P.
		Cells	520	344	134	118	211	46	4		
13	L.V.W.	Treated for meningitis one day and supplied no significant data for this table									P.M.
14	W.O.D.	Pres.	424 mm.	160	240	150	200	170	180	Living	
		Prot.	245 mg.	175	700	725	450	425	302		
		Sugar	36 mg.	48	52	40	45	47	70		Not
		Cells	348		132	36	12	8	24		conf.

S = Smear. G.P. = Guinea pig. *See Case Report No. 1 for latest findings.
C = Culture. P.M. = Post-mortem.

TABLE 5

Combined Miliary-Meningeal Tuberculosis (Treated Before April 15, 1949

Case No.	Name	Age	Race	Sympt. Pre-RX (Wks.)	DURATION OF RX — For Mil. (Days)	DURATION OF RX — For Mil.-Mgts. (Days)	DURATION OF RX — Total RX (Days)	X-RAY CHANGES — 1st Noted (Wks.)	X-RAY CHANGES — Degree of Improv.	STATUS, 4-15-49 — Living (Days*)	STATUS, 4-15-49 — Dead (Days*)
1	T.S.	29	C	6	80	48	128	9	Mod.		161
2	F.H.	48	W	12	59	1	60	5	Mkd.		60
3	C.L.	29	C	2	61	88	149	8	Mkd.		149
4	J.J.	40	C	10	35	85					
		(2nd course for Mgts. alone)				120	240	4	Clear	438	
5	A.W.	63	C	3	18	10	28				28
6	J.K.	32	W	12	66	55	121	Unchg.	Unchg.		183
7	J.S.	25	C	3	39	42	81	6	Mkd.		81

*Days after streptomycin was first started.

TABLE 6 — Cerebrospinal Fluid Findings
(Combined Miliary-Meningeal Tuberculosis)

Case No.	Name	Pre-RX		DAYS AFTER START OF STREPTOMYCIN 0-15	15-30	30-60	60-90	90-120	120-180	180-240	240-300	300-360	Diag. Conf. by
1	T.S.	Pres.	320 mm.			350	Died						
		Prot.	272 mg.	385		800							
		Sugar	41 mg.	27	33.3	56.5							C x 6
		Cells	49	48	12	42							P.M.
2	F.H.	Omitted. Died on first day of treatment for combined miliary-meningeal tuberculosis and supplied no significant data for this table.											
3	C.L.	Pres.	170 mm.	160	275	270	Died						S
		Prot.	125 mg.	82	140	145							C
		Sugar	32 mg.	51	59	42							G.P.
		Cells	356	100	212	48							
4	J.J.*	Pres.	180 mm.	150	150	150	160	300	160	140	130	125	
		Prot.	360 mg.	390	216	386	528	580	625	390	185	95	C x 2
		Sugar	20 mg.	20	41	53	52	58	34	54	63	74	
		Cells	223	352	328	924	96	334	368	207	32	28	
5	A.W.	Omitted. Died on 10th day of treatment for combined miliary-meningeal tuberculosis and supplied no significant data for this table.											
6	J.K.	Pres.	340 mm.	370	450	430		Died					
		Prot.	70 mg.	140	498	800							C x 3
		Sugar	47 mg.	30	25	20							
		Cells	14	96	10	53							
7	J.S.	Pres.	110 mm.	85	600	Died							
		Prot.	85 mg.	89	375								C x 3
		Sugar	48 mg.	53	15								
		Cells	18	10	192								

S = Smear. G.P. = Guinea pig. *See Case Report No. 2 for latest findings.
C = Culture. P.M. = Post-mortem.

were similar to those in the group of patients with tuberculous meningitis alone.

Roentgenological Changes (Table 5): One patient died 28 days after treatment for miliary tuberculosis was started and there were no x-rays available for comparison. In the remaining six patients, there was marked to complete clearing in four (66.7 per cent), moderate clearing in one, and no change in one. It should be noted that there was marked clearing in the x-ray of one patient (No. 2), previously mentioned, who was treated for 59 days on a daily dosage of 0.5 gm. streptomycin for tuberculous laryngitis before miliary tuberculosis and tuberculous meningitis were recognized.

Cerebrospinal Fluid (Table 6): Two patients, who died on the first and 10th day of therapy respectively, did not supply sufficient data to be included in Table 6. Prior to therapy, the spinal fluid pressure was elevated in all cases except one (No. 7). The protein content and the cell count were elevated and sugar was lowered in all cases before therapy. Only one patient (No. 4) showed definite and sustained improvement in all elements during and since treatment ended (see Case Report No. 2).

One patient (No. 7), who was under streptomycin treatment for miliary tuberculosis, revealed tubercle bacilli on culture of a specimen of cerebrospinal fluid in which no other abnormal elements were found. This specimen was obtained during a routine spinal tap at a time when no symptoms suggestive of tuberculous meningitis were apparent. Two weeks after the tap was performed, the patient developed headache—the first symptom suggestive of meningitis. Treatment was changed to the miliary-meningeal regimen. The patient died six weeks later and necropsy confirmed the clinical diagnosis. This case demonstrates the long incubation period of tuberculous meningitis. The two patients who survived more than 14 months will now be described in greater detail.

Case No. 1: F.McC., Reg. No. 203 452 (No. 6 on Tables 3 and 4), a 23 year old white male was admitted February 2, 1948 with a diagnosis of far advanced pulmonary tuberculosis with multiple cavities and hyperactive deep reflexes. Spinal tap revealed the cerebrospinal fluid under pressure of 200 mm. with protein 492 mg., sugar 30 mg., cells 66 per cc. (lymphocytes 80 per cent, neutrophils 20 per cent), chlorides 656 mg. No tubercle bacilli were found on smear, culture, or guinea pig inoculation.

He received 2.0 gm. streptomycin intramuscularly, daily, 0.05 gm. intraspinally three times per week, and 4.0 gm. promin intravenously, daily, from February 4, 1948 to June 3, 1948. Promin was omitted every third week. His temperature dropped to normal. Headache and nuchal rigidity disappeared. The diagnosis was confirmed by inoculation of a guinea pig with cerebrospinal fluid taken two months after cessation of therapy. During the second month of therapy, pain and weakness of the right lower extremity appeared and this cleared completely two months later.

This patient was clinically well 14 months after the beginning or 10 months after the termination of therapy. A specimen of cerebrospinal fluid obtained April 4, 1949, 10 months after completion of treatment, revealed the following: pressure 130 mm., proteins 68 mg., sugar 87 mg., cells 6 (lymphocytes), chlorides 715 mg. Tubercle bacilli were not found on the last eight monthly examinations. All specimens were examined by smear, culture, and guinea pig inoculation.

Case No. 2: J.J., Reg. No. 202 563 (No. 4 on Tables 5 and 6), a 39 year old Negro was admitted on January 24, 1948, acutely ill, with a temperature of 102 degrees F. X-ray film of the chest revealed generalized

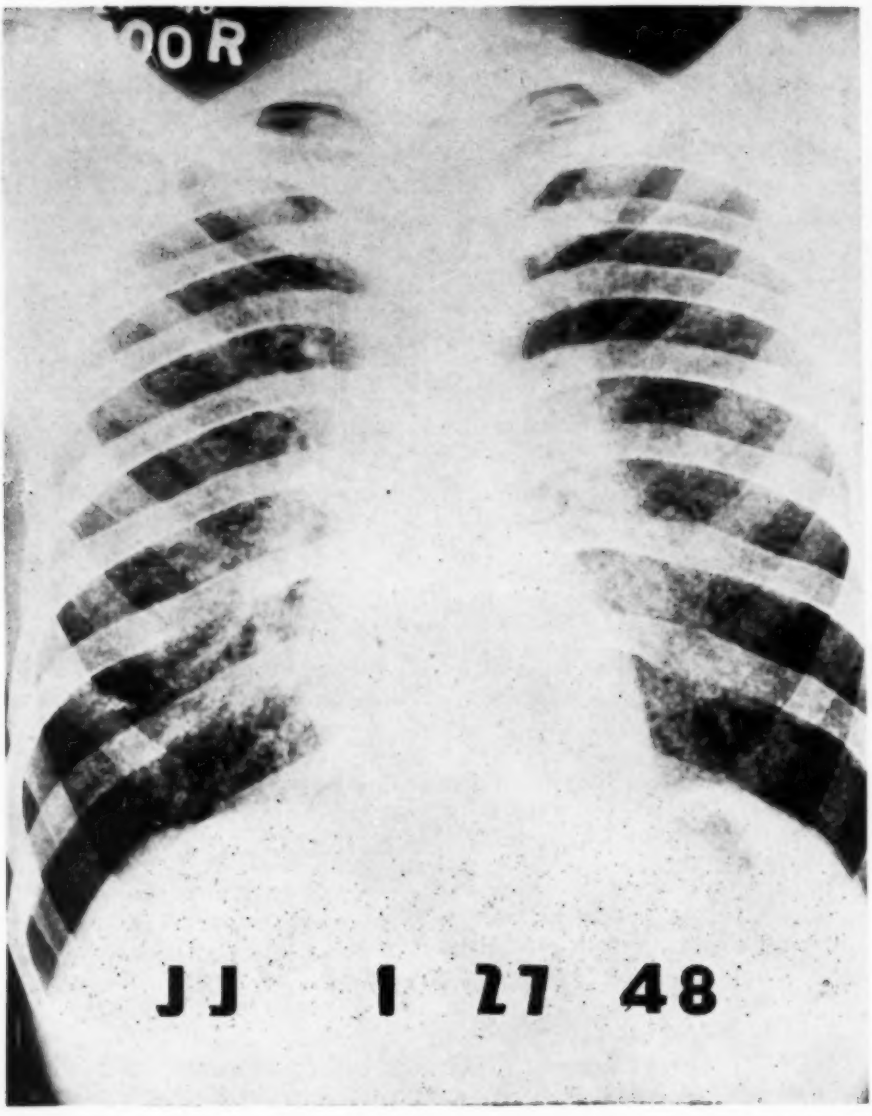

FIGURE 1a: Extensive miliary seeding at beginning of streptomycin therapy. This was followed by tuberculous meningitis 35 days later when treatment was changed to the miliary-meningitis regimen.

miliary tuberculosis (Fig. 1). He received 1 gm. streptomycin intramuscularly and 4 gm. promin intravenously, daily, omitting promin every third week, until tuberculous meningitis was diagnosed on the 35th day of therapy, at which time treatment was changed to the miliary-meningeal regimen and continued for the remainder of 120 days. This resulted in complete clearing of the pulmonary dissemination by the fifth month of therapy and disappearance of all symptoms and neurological findings suggestive of meningitis (Table 6). Relapse of meningeal symptoms occurred two months after termination of his first course of treatment and he was retreated for four months on the meningitis regimen (not on the combined miliary-meningeal regimen). He quickly responded to

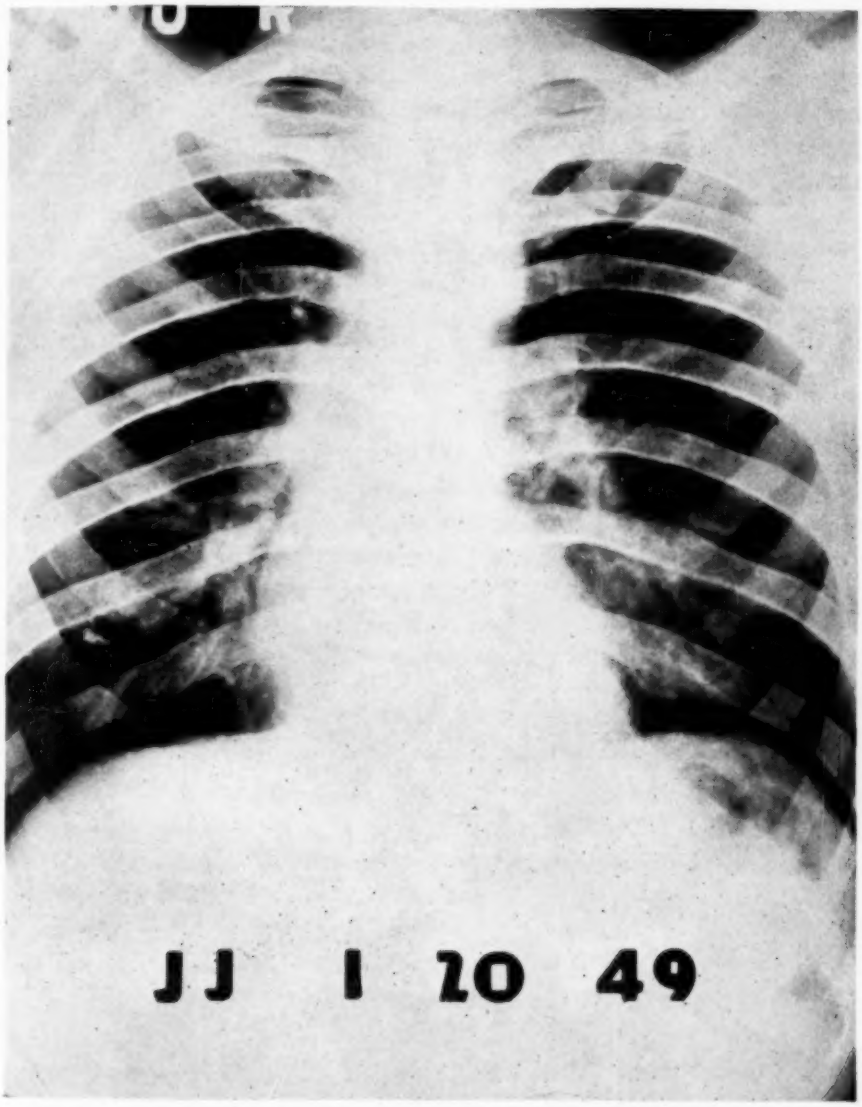

FIGURE 1b: Continuous clearing of pulmonary lesions has taken place simultaneously with the appearance of symptoms of meningitis followed successively by remission, relapse, and remission again on retreatment.

retreatment and was clinically well and free of symptoms 14 months after the beginning of treatment or five months after termination of retreatment.

A specimen of cerebrospinal fluid obtained March 24, 1949, five months after termination of retreatment, revealed the following: pressure 125 mm., protein 100 mg., sugar 87 mg., cells 0, chlorides 718 mg. Tubercle bacilli were not recovered on numerous examinations during the past eight months.

Discussion

Due to the acute nature of miliary tuberculosis and its rapid evolution, the general symptoms usually dominate the clinical picture and the true nature of the disease may not be discovered until quite late. A considerable number of such patients are therefore apt to reach the tuberculosis ward in an almost moribund state. The three deaths in this group of nine patients occurred within 37 days after beginning of therapy and there were no late deaths (Tables 1 and 2).

Quite a different picture is presented by the meningeal cases. Of the 14 patients with meningitis alone (Table 3), 11 died and the three survivors still have abnormal cerebrospinal fluids and are considered in remission. Of the seven patients with combined miliary-meningeal tuberculosis, six died and one is living 14 months after beginning of therapy (Table 5). He is free of symptoms but his cerebrospinal fluid is still abnormal (Case Report No. 2).

Our early enthusiasm concerning the value of streptomycin in the treatment of tuberculous meningitis was considerably dampened as one after another of the patients who were apparently on their way to recovery ceased responding to the drug, gradually lapsed into coma or developed some complications, and died. And, judging by our own experiences, the same fate was probably met by many of the cases reported as cures in the literature.

Yet, regardless of the paucity of permanent and complete recoveries, the value of this drug against tuberculous meningitis should not be underestimated. Rather, we must search for means of enhancing its action. In our disappointment over relapses in the majority of cases treated, we are liable to lose sight of the fact that we are dealing with a disease which was heretofore 100 per cent fatal in about two to eight weeks, and in which remissions were practically unknown. Notwithstanding the eventual fatal issue, the favorable early therapeutic response and the unprecedented survival for many months, to more than a year in many cases, are in themselves great achievements and prove the effectiveness of the drug up to a certain point. One must now look for the reason why streptomycin, which is so effective a therapeutic agent against tuberculous meningitis at first, fails eventually

in most of the cases. Somewhere along the line streptomycin loses its potency. At what point does this change take place, and why?

Bacterial resistance undoubtedly plays its role in limiting the effectiveness of streptomycin in tuberculous meningitis, but, presumably, to no greater extent than it does in other forms of tuberculosis. It is natural to suspect, then, that the condition which limits the effectiveness of the drug in this type of tuberculosis may lie not in the bacterial agent but may be inherent in the normal and pathological anatomy of the organ involved.

Particularly impressive are the following facts: (a) no recurrence of pulmonary seeding was observed in any of our miliary cases; (b) no pulmonary seeding was observed in any of our patients who developed tuberculous meningitis first; (c) none of our patients with uncomplicated miliary tuberculosis died of this disease if he survived six weeks under streptomycin therapy; (d) none of our patients with miliary tuberculosis developed meningitis if he did not exhibit symptoms of meningitis during the first two months of streptomycin therapy, and (e) clearing of the miliary lesions, from moderate to complete, was observed, regardless of streptomycin dosage, in five of six patients with combined miliary-meningeal disease who survived long enough to be x-rayed 42 days after beginning of streptomycin therapy, even though the meningitis proved fatal in all but one patient.

How shall we account for the marked effectiveness of the drug to apparently control the lesions in the lungs and the apparent ineffectiveness to accomplish the same purpose in the central nervous system? How shall we explain the freedom from relapses in the lungs and the frequent relapses in the central nervous system? If successive seedings are responsible for relapses in meningitis, why should the lungs have uniformly escaped reseeding? What role, if any, do successive seedings play in the occurrence of relapses? Our knowledge of the action of streptomycin and of its effect on different types of tuberculous lesions leads us to believe that when streptomycin fails to materially benefit a tuberculous lesion in a patient, who is not moribund, and whose organisms are not resistant, it is frequently due to the inability of the drug to make effective contact with the tubercle bacilli The answer to these perplexing questions may possibly be found, to some extent, in different sources of dissemination with different degrees of accessibility of the tubercle bacilli to the action of this antibiotic.

Zollinger,[25] in his report of 22 necropsies, observed evidence of sclerosing meningitis in cases of "subacute and chronic" tuberculous meningitis treated with streptomycin. On the other hand, Baggenstoss, Feldman, and Hinshaw[26] emphasize the fact that they

observed no evidence of healing in the hematogenous lesions of the brain in four patients who died of miliary-meningeal tuberculosis, although there was definite evidence of healing in the miliary tubercles of the lungs, liver, and spleen. These authors further note that, when the concentration of streptomycin was determined in various tissues and body fluids in one of their cases which came to autopsy, a considerable amount of the drug was found in all specimens examined except the brain, and although 15.8 mcg. per ml. was found in the spinal fluid, no streptomycin was detected in the brain tissue. Adcock and Hettig[27] reported finding no streptomycin in the brain and liver in one case of tuberculous meningitis treated with streptomycin and a trace in another case, while finding appreciable amounts of the drug in other tissues and body fluids.

Pursuing the same line of investigation, Wallace and his coworkers[28] studied the effects of adding streptomycin in equal amounts to three different culture media, one of which consisted of a brain-heart infusion. They found that *Eberthella typhosa* and *Staphylococcus aureus* grew well in the brain-heart infusion, but decreased in number in the other cultures, thus suggesting that there is something in the brain-heart infusion which has the property of rendering streptomycin ineffective.

Continuing further on the trail of the streptomycin inhibiting factor, Rhymer and Wallace[29] located it finally in a brain infusion from which they apparently succeeded in extracting it. Since brain tissue is thus shown to possess antistreptomycin activity in vitro, it is logical to suspect that something else than the hematoencephalic barrier may account for the absence of streptomycin in the brain when it was present in other organs.[26,27]

Whether a particular case of meningitis is due to hematogenous seeding of the meninges or to direct extension from a cortical caseous focus or, possibly, to seeding from a focus elsewhere in the body, it is always secondary to an older caseous focus.

Certain pathological and clinical evidences suggest the probability that streptomycin may not penetrate to a significant extent into the larger caseous masses: (a) this drug is usually most effective on surface lesions where necrotic material easily separates and is cast off; (b) it seems least effective on tuberculous lesions of internal organs where large caseous masses remain locked up for a considerable time or indefinitely; (c) this antibiotic has a profound effect on miliary tuberculosis where individual areas of caseation, if present, are minute and are apparently more accessible to the drug than the larger ones; (d) streptomycin is carried through the blood stream and there is no blood supply to the caseous masses.

If it is true that streptomycin does not penetrate the avascular necrotic mass of the caseous tubercle in effective concentration, the tubercle bacilli usually found in such lesions would be comparatively safe from the action of this antibiotic. The greater the area of caseation, the safer are probably the tubercle bacilli within it.[26] And, when the caseous focus happens to be located in the brain, the tubercle bacilli within may have a double defense: the caseous mass as well as the antistreptomycin factor in the brain tissue.

If this hypothesis is correct, more effective therapy of tuberculous meningitis would depend primarily, upon devising means for overcoming the antistreptomycin factor in the brain and, secondarily, upon finding a way of carrying the drug into the caseous foci in therapeutic concentration. Attempts to overcome these obstacles have been made and a ray of hope is visible.

Nelson and his co-workers[30] have shown that streptomycin mixed with trypan blue and injected into guinea pigs was retained in the liver and spleen in appreciable quantities as long as 25 hours after the injection. On the other hand, when streptomycin unmixed with trypan blue was injected into guinea pigs, a small amount of it was found in the liver one hour after injection, but no streptomycin was detected in this organ four hours after, or in the spleen at any time. However, Bogen's[31] attempt to treat tuberculous guinea pigs using streptomycin mixed with trypan blue produced entirely negative results.

Based on the work of Jobling and Petersen,[32] who showed that iodine is able to bring about the liquifaction of caseous material and the subsequent liberation of tubercle bacilli held within it, Woody and Avery[33] treated one group of tuberculous guinea pigs with streptomycin alone and another group with both streptomycin and potassium iodide. They found that the mortality in the two groups at the end of 12 weeks of treatment was six out of 13 with streptomycin alone and two out of 14 with streptomycin and potassium iodide.

The use of streptomycin in combination with streptokinase has considerably improved the results from the treatment of tuberculous meningitis in the experience of Cathie[34] who states that streptokinase helps to bring about lysis of the fibrin clots, frequently found at the base of the brain in patients who died of tuberculous meningitis, and thereby enables the streptomycin to make contact with the, usually, sensitive organisms found in these clots. In two small groups of patients treated, the recovery rate was 21 per cent with streptomycin alone and 58 per cent with streptomycin and streptokinase combined.

Experience with the use of streptomycin in the treatment of

various forms of tuberculosis[35] has given ample proof that if this drug is effective at all it is usually as effective with 1 gm. as it is with higher doses. Our own studies reveal that 1 gm. streptomycin is highly effective in miliary tuberculosis. The multiplicity of regimens employed in the treatment of tuberculous meningitis, the apparent lack of a consensus as to what constitutes the optimum regimen, an analysis of the reported results, as well as our own observations, seem to indicate that, with the possible exception of intrathecal medication, the effects of therapy in this disease have heretofore not varied conspicuously with the different dosages of streptomycin generally employed, whether alone, or in combination with other drugs. It may therefore appear futile to expect better results than heretofore by continuing the attacks on tuberculous meningitis with higher doses of streptomycin. Until another and more effective antibiotic against tuberculosis is discovered, we should change our mode of attack on this problem and aim our efforts primarily at finding means of penetrating more effectively the defenses behind which the tubercle bacilli may find protection in the human body. We must enable the drug to make adequate contact with the organism wherever it may be. The experiments with trypan blue, iodides, and with streptokinase seem to be steps in the right direction.

It seems likely that the cases of tuberculous meningitis in which an apparently permanent cure is obtained may have originated from a tuberculous focus outside the brain wherein the tubercle bacilli have possibly only one line of defense—the caseous mass. On the other hand, the majority of cases, the ones that succumb to the disease sooner or later, may have been caused by lesions in the brain where the organisms have possibly a fairly effective double defense system. The initial remission of symptoms in these cases could be due to the ready contact streptomycin is able to make with the tubercle bacilli in the more accessible areas and organs involved, all of which play their respective parts in contributing to the overall clinical picture.

SUMMARY AND CONCLUSIONS

1) Streptomycin seems effective in the treatment of uncomplicated cases of miliary tuberculosis. This could be accounted for by the small size of the individual tubercle which may permit the drug to readily penetrate throughout the lesion in therapeutic concentration and to come in direct contact with all the organisms, a condition which probably does not exist where larger areas of caseation are present.

2) Streptomycin did not prevent the development of tubercu-

lous meningitis in patients while they were under treatment with the same drug for other tuberculous conditions.

3) It seems possible that the main obstacles to successful therapy of tuberculous meningitis may be: (a) a factor in the brain, presumably, yet unidentified, which has the property of inhibiting streptomycin and thus rendering it ineffective; and (b) the relative inability of streptomycin to penetrate the larger caseous foci.

4) Until a more effective antibacterial agent against tuberculosis may be discovered, efforts will undoubtedly be continued to identify the streptomycin inhibiting factor in the brain, and to find means of combating it. Further search is also indicated for some means of more effectively carrying the therapeutic agent into the caseous masses.

5) Our experiences thus far lead us to believe that higher doses of streptomycin would probably not materially improve the results in tuberculous meningitis and in combined miliary and meningeal tuberculosis. It does not seem likely that the streptomycin inhibiting factor in the brain and the conditions which seem to prevent the drug from entering the caseo-necrotic mass in therapeutic concentration, could be overcome with relative safety by sheer volume of this antibiotic.

Acknowledgment: Grateful acknowledgment is made to Dr. Arthur M. Walker, Secretary of the Veterans Administration Central Office Streptomycin Committee, who kindly reviewed our manuscript and made many helpful suggestions.

RESUMEN Y CONCLUSIONES

1) La estreptomicina parece efectiva en los casos de tuberculosis miliar no complicados. Esto puede atribuirse al pequeño tamaño del tubérculo individual lo que puede permitir a la droga penetrar a través de la lesión en un grado de concentración terapéutica y ponerse en contacto con todos los gérmenes, lo que probablemente no ocurre cuando hay áreas de caseificación.

2) La estreptomicina no evitó el desarrollo de la meningitis tuberculosa en enfermos que estaban bajo el tratamiento con estreptomicina por otras localizaciones tuberculosas.

3) Parece que los obstáculos más importantes para el tratamiento efectivo de la meningitis tuberculosa pueden ser: (a) un factor en el cerebro probablemente aún no identificado que tiene la propiedad de inhibir la estreptomicina convirtiéndola en ineficaz; y (b) la relativa incapacidad de la estreptomicina para penetrar dentro de los focos caseosos más grandes.

4) Mientras no se encuentre otro agente antibacteriano más eficaz contra la tuberculosis, sin duda que continuarán los esfuerzos para identificar el agente inhibidor en el cerebro y para

encontrar el modo de contrarrestarlo. También se requieren medios para introducir más eficazmente el agente en los focos caseosos.

5) Hasta ahora nuestra experiencia nos conduce a pensar que las dósis más altas de estreptomicina no mejorarían materialmente los resultados en la meningitis tuberculosa y en la combinación de tuberculosis miliar y meningitis.

No parece posible que el factor inhibiente cerebral y las condiciones que evitan el acceso de la estreptomicina dentro de las masas caseonecróticas pueda dominarse mediante gran aumento de volumen del antibiótico.

REFERENCES

1 Cooke, R. E., Dumphy, D. L. and Blake, F. G.: "Streptomycin in Tuberculous Meningitis; A Report of Its Use in a One Year Old Infant," *Yale Jour. Biol. and Med.*, 18:221, 1946.
2 Applebaum, Emanual and Halkin, Cyrille: "Tuberculous Meningitis and Miliary Tuberculosis Arrested with Streptomycin," *J.A.M.A.*, 135: 153, 1947.
3 Mehas, C. P. and Truax, Wayne E.: "Streptomycin in Tuberculous Meningitis," *J.A.M.A.*, 135:155, 1947.
4 Bauer, Richard B. and Sauer, Elmer P.: "Streptomycin in Tuberculous Meningitis," *Dis. of Chest*, 14:843, 1948.
5 Hinshaw, Corwin H., Feldman, Wm. H., Pfuetze, Karl H.: "Treatment of Tuberculosis with Streptomycin: A Summary of Observations on One Hundred Cases," *J.A.M.A.*, 132:778, 1946.
6 Hinshaw, C. H.: Personal communication.
7 Cocchi, Cesare and Pasquinucci, Gaetano: "Primi resultati nella terapia delle meningiti tubercolari con la streptomicina associata a solfone e vitamin A," *Revista di Clinica Pediatrica*, 45:193, 1947.
8 Debré, R., Thieffry, et Brissau, E.: "Méningite tuberculeuse et tuberculose miliare aigue chez l'enfant traité par la streptomycine," *Presse Med.*, 56:121, 1947.
9 Ibid: "La streptomycine appliquée au traitement de la méningite tuberculeuse et de la tuberculose miliare chez l'enfant," Paris, 1948.
10 Debré, R., Brissaud, E. et Neufflard, H.: "Streptomycin and Tuberculous Meningitis in Children," *Brit. Med. Jour.*, 2:897, 1947. Also abstracted in *J.A.M.A.*, 136:723, 1948 and commented on in *New Letter*, p. 841, ibid., March 20, 1948.
11 Decourt, J.: "En 72 cases de méningite tuberculeuse traités par la streptomycine," *Presse Med.*, 56:129, 1948.
12 Fouquet, Jean: "Streptomycine et tuberculose," *Presse Med.*, 56:131, 1948.
13 DeLavergne, V.: "Le centre de streptomycine de Nancy," *Presse Med.*, 56:132, 1948.
14 Mouriquand, G.: "Le centre de streptomycine de Lyon (enfants)," *Presse Med.*, 56:133, 1948.
15 Cathala, J., et Bastin, R.: "Premiers essais de traitement par la streptomycine en médicine infantile," *Presse Med.*, 56:119, 1948.
16 Sédallian, P., et al: "La centre de streptomycine de Lyon (adultes)," *Presse Med.*, 56:134, 1948.
17 Bernard, Etienne, Bernard, B. Kreis, Lotte, Alice: "Sur la traitement de la tuberculose de l'adult par la streptomycine," *Presse Med.*, 56: 118, 1948.
18 Bernard, Etienne: Personal communication to Dr. Hinshaw.
19 Van Goidsenhoven, Fr., Stevens, R. and Crolla, P.: "La streptomycine dans la méningite tuberculeuse et dans la tuberculose miliare aigue," *Bull. de L'Accad. Roy de Med. de Belg.*, 13:292, 1948.
20 Marshall, G., et al: "Streptomycin Treatment of Tuberculous Meningitis," *Lancet*, 254:583, 1948.
21 Loffler, W. and Piotti, A.: "Streptomycin und tuberkulose," *Basel*, p. 55, 1948.

22 Lincoln, Edith M., Kirmse, Thomas W. and DeVito, Estelle: "Tuberculous Meningitis," *J.A.M.A.*, 136:593, 1948.
23 Bunn, Paul: "One Hundred Cases of Miliary and Meningeal Tuberculosis Treated with Streptomycin," *Am. Jour. Med. Sciences*, 216:286, 1948.
24 Smith, H. V., Vollune, R. L. and Cairns, Sir Hugh: "Treatment of Tuberculous Meningitis with Streptomycin," *Lancet*, 254:627, 1948.
25 Zollinger, H. U.: "Streptomycin und tuberkulose," *Basel*, p. 293, 1948.
26 Baggenstoss, A. H., Feldman, W. H. and Hinshaw, H. C.: "The Effect of Streptomycin on the Pathology of Generalized Miliary and Meningeal Tuberculosis," *Proceedings of the Staff Meetings of the Mayo Clinic*, 22:265, 1947.
27 Adcock, J. D. and Hettig, R. A.: "Absorption, Distribution and Excretion of Streptomycin," *Archives of Int. Med.*, 77:179, 1946.
28 Wallace, G. I., Rhymer, I., Gibson, O. and Shattuck, M.: "Studies in the Mode of Action of Streptomycin. I. Effect of Culture Media," *Proceedings of the Society for Experimental Biology and Medicine*, 60:127, 1945.
29 Rhymer, I. and Wallace, G. I.: "Studies on the Mode of Action of Streptomycin. II. The Nature of a Streptomycin Inhibitor Occurring in Brain Tissue and Plant Extracts," *Jour. of Bacteriology*, 54:521, 1947.
30 Nelson, W. E., Forgacs, J. and Kucera, J. L.: "Alteration of the Distribution and Excretion of Streptomycin," Proceedings *of the Society for Experimental Biology and Medicine*, 64:20, 1947.
31 Bogen, E.: "Distribution of Streptomycin in the Treatment of Tuberculosis," *Rivista Panamericana de Medecina y Cirugia del Torax*, 1: 171, 1948.
32 Jobling, J. W. and Petersen, W.: "A Study of the Ferments and Fermentinhibiting Substances in Tuberculous Caseous Material." *J. Exp. Med.*, 19:383, 1914.
33 Woody, Edgar Jr. and Avery, Roy C.: "The Combined Effect of Potassium Iodide and Streptomycin on Established Tuberculosis in Guinea Pigs," *Science*, 108:501, 1948.
34 Cathie, J. A. B.: "Streptomycin-streptokinase Treatment of Tuberculous Meningitis," *The Lancet*, 1:441, 1949.
35 Streptomycin Committee, Veterans Administration: "Streptomycin in the Treatment of Tuberculosis. Report to Council on Pharmacy and Chemistry," *J.A.M.A.*, 138:584, 1948.

Discussion

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The experience in our department under the supervision of Dr. Robert High has been similar to that of Dr. Shamaskin and his group. Dr. High has had approximately two-thirds the number of patients (infants and children) under treatment reported in this series by Dr. Shamaskin, but there is no significant difference in the results. To the best of my knowledge, these results reflect the experience of other investigators now working in this country with the exception of Edith Lincoln at Bellevue Hospital. Her results, reported recently before the American Pediatric Society, are better than those obtained in other clinics. The reasons for the more favorable results in her series are not apparent. While there are certain differences in her plan of therapy as compared with that of others, these would not appear to be significant. Her ther-

apeutic regime includes 1 gram of streptomycin per day intramuscularly for a period of six months, 100 mgms. of streptomycin intrathecally for 40 daily doses for 40 days (sometimes 50 mg. every other day for 40 doses), and promizole over a period of three years. The plan of therapy now employed by Dr. High in conjunction with several other clinics who are cooperating in a study under the auspices of the Tuberculosis Control Division of the U. S. Public Health Service is as follows: 50 mgms. of streptomycin per Kg. of body weight every 12 hours; promizole, 1 gram per day to infants under six months and 2 grams per day to patients over six months of age. In addition to these two agents, alternate cases receive 0.2 gm./Kg. of body weight per day of para-aminosalicylic acid. Streptomycin is administered for a period of six weeks with a rest period of 10 days, and repetition if there is still any evidence of tuberculous activity. Promizole and para-aminosalicylic acid are continued for a period of six months. The principal differences in relation to Dr. Lincoln's plan are: (1) She administers streptomycin for a period of six months; (2) Promizole, over a period of three years; and (3) she does not use para-aminosalicylic acid. There is no essential difference in the total daily dosage of streptomycin that is employed by the two groups. The principal difference would appear to be in the length of time that she continues Promizole. However, since most of the deaths in our clinic have occurred during the course of therapy this would not appear to be a deciding factor. Since most of her patients come from her own Out-Patient Dispensary it may be that treatment is started materially earlier in the course of the disease than it has been in other clinics such as ours where practically all of the cases are referred and at a time when the disease is well advanced.

It has been suggested but not proved that promizole may retard the development of resistance of the tubercle bacillus to streptomycin. At the moment we do not have data pertinent to this question but in one instance marked increase in the resistance of the tubercle bacillus to streptomycin was observed in a child who was receiving diazone in conjunction with streptomycin for the therapy of miliary tuberculosis and tuberculous meningitis. In the initial episode when there was an apparent remission of both the pulmonary and meningeal lesions, the tubercle bacilli were susceptible to streptomycin; subsequently during an exacerbation of the meningitis, from which the child died, the tubercle bacilli were quite resistant. The use of adjunct substances to enhance the effectiveness of streptomycin would seem to be the most likely possibility of an improvement in therapy at the moment. Our experience with para-aminosalicylic acid in this relation does not permit critical evaluation but it seems doubtful that it will

make any significant difference in the treatment of tuberculous meningitis.

A search for substances which would materially enhance the effect of streptomycin in nervous tissue would seem to be important on the basis of present leads. Whether iodides will have a significant effect in making tubercle bacilli available from caseous foci is yet to be demonstrated, but is worthy of further investigation. The availability of a substance which would retard development of resistance by tubercle bacilli to streptomycin would seem to be an essential feature of long continued streptomycin therapy. While antibiotics more effective than streptomycin, e.g., neomycin, against tubercle bacilli may be forthcoming, the problem of reaching tubercle bacilli implanted in non-vascular caseous foci remains a factor of first importance.

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I want to emphasize Dr. Shamaskin's statement that age of the patient, duration of the disease, method of treatment and period of post therapy observation are factors which influence the results of the treatment of tuberculous meningitis with streptomycin. There is still, however, no clear-cut pattern of these influences and still no uniformity of opinion concerning the use of intrathecal therapy, the amount of drug to be used or the duration.

To add to this picture, and I hope not confuse it further, I should like to present data gathered from the use of streptomycin in the treatment of tuberculous meningitis in Detroit. For these statistics I am indebted to Dr. Donald C. Young of Herman Kiefer Hospital and Dr. Edna M. Jones of Maybury Sanatorium.

Slide Descriptions

Slide I shows that of 84 cases—61 or 73 per cent expired and 23 or 27 per cent recovered. The highest rates of deaths were among whites, females and adults.

Slide II shows that the patients who expired ranged from four months to 55 years but that no recoveries occurred in patients under ten months or over 35 years of age. Other factors influencing the recovery were freedom from miliary and other forms of tuberculosis. Thirty-three per cent of the expired cases had miliary tuberculosis in comparison with 13 per cent of the recovered cases. Seventeen per cent of the recovered cases had no other lesions as compared to six per cent of the expired cases. The duration of illness prior to the start of therapy was significantly different:

an average of 22 days had elapsed in the expired cases as compared to 13 days in the recovered cases and in nine selected cases in which therapy was instituted within 30 hours of the onset of symptoms there were no deaths.

Slide III shows that there was no significant difference in the intramuscular streptomycin dosage between those which expired and those which recovered.

Slide IV shows that 80 per cent of the patients treated with intramuscular streptomycin alone expired and 68 per cent of those who also received intrathecal streptomycin expired.

Slide V shows that there was no significant difference in the intrathecal dosage between those who expired and those who recovered except that the same nine selected cases were treated for a period of 163 days instead of 80 days and consequently received a greater total amount of streptomycin. When these nine selected cases are removed from the recovered combined therapy group, the recovery rate of the remainder is no better than in the group treated with intramuscular therapy alone.

With these statistics it would seem that we have a fairly strong case for early combined therapy and for prolonged treatment of both intramuscular and intrathecal varieties. Best results are obtained in the earlier treated cases and this is so important that I feel in doubtful cases one should err on the side of starting treatment early even at the expense of being required to explain a false start. This applies also to the use of intramuscular streptomycin in miliary tuberculosis. A small amount of streptomycin given while the diagnosis is being confirmed will probably do little or no harm and may mean the difference between success and failure of therapy.

How long does meningitis retain its responsiveness to streptomycin? At what stage of development is it no longer possible to get benefit from streptomycin? From our data it would seem that 21 days is beyond the point and 13 days is somewhere near the point of maximum duration of the disease when streptomycin may still be effective. Is it possible to enhance the effect of streptomycin with other drugs? We have no answers except that promizole and PAS are not tolerated well by children, that dihydrostreptomycin used in 12 meningitis cases produced startlingly bad results in all and that 10 meningitis cases now dead were treated with iodides without apparent benefit. Relapses will occur; however, I believe they will be less in evidence when prolonged treatment is used.

I compliment Dr. Shamaskin and his associates for their splendid work.

The Treatment of Tuberculous Tracheobronchitis with Streptomycin

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Introduction

Tuberculous tracheobronchitis is a frequent and important complication or concomitant finding in pulmonary tuberculosis. The stage, extent and course of the pathological bronchial changes usually determine the type of therapeutic procedures to be used for the control of the pulmonary tuberculosis. Treatment of tuberculous tracheobronchitis was unsatisfactory prior to the use of streptomycin. The prevention of chronic bronchial changes, such as tuberculous bronchiectasis and fibrostenosis, will solve many of the therapeutic problems of pulmonary tuberculosis. Successful control of the serious effects of tuberculous tracheobronchitis is essential to obtain satisfactory end results in the treatment of pulmonary tuberculosis.

Early reports by Brewer and Bogen,[1] and O'Keefe[2] indicated that ulcerogranulomatous lesions of the trachea and major bronchi responded well to combined intramuscular and inhalation treatment with streptomycin. Subsequently, inhalation therapy with streptomycin was found to be irritating and generally its use has been discarded. Pfuetze and Pyle[3] state, "Almost without exception, ulcerating and granulomatous lesions of the oropharynx, larynx and tracheobronchial tree have healed within a few weeks when streptomycin was administered." Tucker[4] reports, "The effect of streptomycin on tuberculous lesions of the mucosa of the larynx and tracheobronchial tree is striking." The excellent cooperative study by the Veterans Administration, Army and Navy[5] on the effects of streptomycin in the treatment of tuberculosis proves rather conclusively that this drug, in varying doses and regimens, is capable of producing improvement in tuberculous tracheobronchitis and tuberculous laryngitis in 80 to 90 per cent of the cases selected for treatment.

Material

Clinical study of 25 patients with proved tuberculous bronchitis is the basis for this report. It is recognized that a presumptive diagnosis of tuberculous tracheobronchitis may be made on the

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basis of clinical and roentgenological findings but only those patients with demonstrable lesions in the major bronchi, as observed bronchoscopically, were included in this study.

The pathological changes observed consisted primarily of ulcerations and granulations with associated hyperemia, edema and infiltration. Those patients who demonstrated only hyperemia, submucous tubercles or slight edema and infiltration were not considered as proved cases. Patients were also excluded if the bronchial tuberculosis had progressed to the stage of apparently healed fibrostenosis.

Bronchoscopic examinations were performed on all of the patients prior to the institution of treatment with streptomycin. Reexaminations were performed at intervals of two to four weeks during treatment and sufficiently often after therapy to determine the subsequent course. All of the bronchoscopic observations were made by the same bronchoscopist so that interpretation of the pathological changes and the results of treatment with streptomycin was uniform.

Treatment

We have been guided, in the main, by the recommendations of the Veterans Administration, Army and Navy in determining the regimens of treatment to be employed. Our earlier cases were given 0.2 gm. or 0.4 gm. of streptomycin by intramuscular injections five times daily for 60 to 120 days. It was soon noted that 1 gm. daily gave results comparable to 2 gm. and the frequency of administration was reduced to every 12 or 24 hours. The duration of treatment has varied from 30 to 120 days.

At the present time 1 gm. of streptomycin dissolved in 2 cc. of normal saline is given daily in a single intramuscular injection. Daily injections are continued for 30 to 90 days. The duration of treatment is determined by the rapidity of healing as observed by bronchoscopic examinations at two to four week intervals.

Plans for the permanent control of the pulmonary tuberculosis, whenever indicated, should be instituted prior to the use of streptomycin. Definitive treatment should be started as soon as feasible while the early beneficial effect of streptomycin is at its peak. Attack on the pulmonary tuberculosis at the earliest possible time is mandatory due to the emergence of resistant strains of tubercle bacilli as a result of treatment with streptomycin. Treatment should be continued only sufficiently long to obtain the desired effects in order to prevent or delay the development of resistant strains.

Results of Treatment

The 25 patients have been observed for a period ranging from

three to 27 months, with an average of 12 months, following completion of treatment with streptomycin. In 12 (48 per cent) of the patients, sputum or gastric cultures were converted from positive to negative. In four (16 per cent) patients, cultures which had converted to negative soon after treatment with streptomycin had been completed subsequently reverted to positive. Tubercle bacilli continued to be found in nine (36 per cent). Streptomycin should not receive the full credit for sputum or gastric conversion since some of the patients were treated subsequently with collapse or resection.

Tuberculous bronchitis was considered healed at the completion of treatment with streptomycin in 12 (48 per cent). In nine (36 per cent) patients the bronchitis was interpreted as showing marked improvement. In three patients slight improvement was noted and in one patient the bronchitis was considered unchanged. However, in two of the patients with slight improvement and in one patient with marked improvement, fibrostenosis subsequently developed.

Seven patients had some form of collapse therapy at the time the tuberculous bronchitis was recognized and in nine others collapse was instituted or resection performed following treatment. Sixteen (64 per cent) were thus aided by some type of collapse or resection in addition to streptomycin.

Comment

Streptomycin is an effective weapon against tuberculous tracheobronchitis. Definitive treatment may now be planned for many patients who formerly were doomed to develop irreversible chronic bronchial and pulmonary changes. Streptomycin must be fitted into a coordinated program of treatment and its use withheld until the optimal time.

The development of resistant strains of tubercle bacilli is the primary drawback to the use of streptomycin. This often precludes its use at a subsequent period when, at times, it may be needed urgently. Toxicity has been reduced to a minor problem since reduction of the standard dosage to 1 gm. daily.

Symptomatic improvement may be dramatic when severe, intractable cough is present. Fever frequently is reduced to normal and there is improvement in appetite and gain in weight. Streptomycin exerts a tonic effect on the general condition.

Streptomycin is not recommended when tuberculous bronchitis has developed to the stage of healed fibrostenosis. Ulcers and ulcerogranulomas respond best and the visible lesions usually heal or show marked improvement within a few weeks. When the diagnosis of tuberculous tracheobronchitis or tuberculous bronchitis is based upon presumptive evidence alone, careful and continued

clinical observation should precede the use of streptomycin and its use should be part of a planned and coordinated attack upon the bronchial and pulmonary tuberculosis.

SUMMARY

1) Streptomycin, in dosage of 1 gm. daily, produced healing or marked improvement in 21 (84 per cent) of 25 patients with acute tuberculous bronchitis.

2) The duration of treatment with streptomycin was determined by repeated bronchoscopic examinations and varied from 30 to 120 days in this series. At the present time treatment seldom exceeds 60 days.

3) Measures to control the associated pulmonary tuberculosis should be instituted as soon as practical after therapy with streptomycin has been completed.

4) Irreversible chronic bronchial and pulmonary changes may be averted by the judicious and timely use of streptomycin.

REFERENCES

1 Brewer, L. A. and Bogen, E.: "Streptomycin in Tuberculous Tracheobronchitis," *Am. Rev. Tuberc.*, 56:408, 1947.
2 O'Keefe, J. J.: "The Use of Streptomycin in Tuberculous Tracheobronchitis," *Ann. Otol., Rhin. and Laryng.*, 57:784, 1948.
3 Pfuetze, K. H. and Pyle, M.M.: "The Use and Misuse of Streptomycin in the Treatment of Tuberculosis," *J. Lancet*, 68:431, 1948.
4 Tucker, W. B.: "Streptomycin in the Treatment of Various Tuberculous Conditions," *J. Lancet*, 68:282, 1948.
5 Streptomycin Committee, Veterans Administration: "Streptomycin in the Treatment of Tuberculosis," *J.A.M.A.*, 138:584, 1948.

Topical Detergent Antibiotics in the Treatment of Tuberculous Sinuses

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Before the era of antibiotic therapy, one of the most difficult medical problems involved the treatment of chronic draining tuberculous sinuses. The advent of streptomycin and its use via the intramuscular route has brought definite clinical improvement, if not complete irradication of the lesion, in a substantial proportion of treated patients.

In 12 cases reported by Brock[1] all but one of a total of 60 tuberculous sinuses were closed by intramuscular streptomycin administered over a period of one to 20 weeks. Streptomycin may, therefore, be regarded as by far the most effective agent for control of chronic tuberculous sinuses. At the same time close examination of the accepted method of administration suggests that certain improvements may be made in the technique of treatment.

Streptomycin therapy for tuberculous sinuses as practiced by Brock consists of the daily administration of 1.8 grams in six divided doses given intramuscularly. Six of his patients were treated for 90 days, and the remaining six for 150 days, with an untreated interval of three weeks following the first 90 days of streptomycin. Toxic reactions, including dizziness, headache and ataxia were observed.

The success of any plan of antibiotic therapy must depend on the production of a sustained inhibitory level of the drug at the site of infection. To this end, the treatment of an infected sinus tract by parenteral therapy represents, in our opinion, a relatively inefficient and wasteful procedure. A small fraction of the quantity of streptomycin required for intramuscular administration should produce a relatively enormous local concentration if introduced directly into the sinus tract where its ultimate activity must take place. The fact that an apparently great degree of efficiency is obtained in using antibiotics topically prompted the senior author to treat a woman suffering from a tuberculous sinus of seven years duration with streptomycin, using a surface active germicide as a solvent. Previous experience with antibiotics administered locally in solutions of reduced surface tension[2-4] indicated a logical extension to include infected sinus tracts of tuberculous origin.

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CASE HISTORY

The patient was a 36 year old white female who learned in August of 1934 that she had advanced pulmonary tuberculosis involving most of her left lung. In November of that year she was started on pneumothorax which was carried on until April of 1937 when she became febrile from infected pleural fluid. In smears and cultures the presence of Mycobacterium tuberculosis was established. Numerous forms of therapy, including thoracoplasty, were tried to control this unfortunate complication but all were unsatisfactory.

In January of 1939, a boggy inflammatory mass developed in the posterior aspect of the left axilla which spontaneously opened and discharged purulent material. Drainage persisted for seven years and nine months. Closure of the sinuses in October of 1946 was then accomplished by the use of topically applied streptomycin with a germicidal detergent.

Seventeen months later, after a severe nasopharyngitis, the patient noted a swelling over the lower portion of the previously closed sinus tract. She was immediately hospitalized after 15 m.l. of pus had been evacuated. Cultures, smears and biopsy of slough

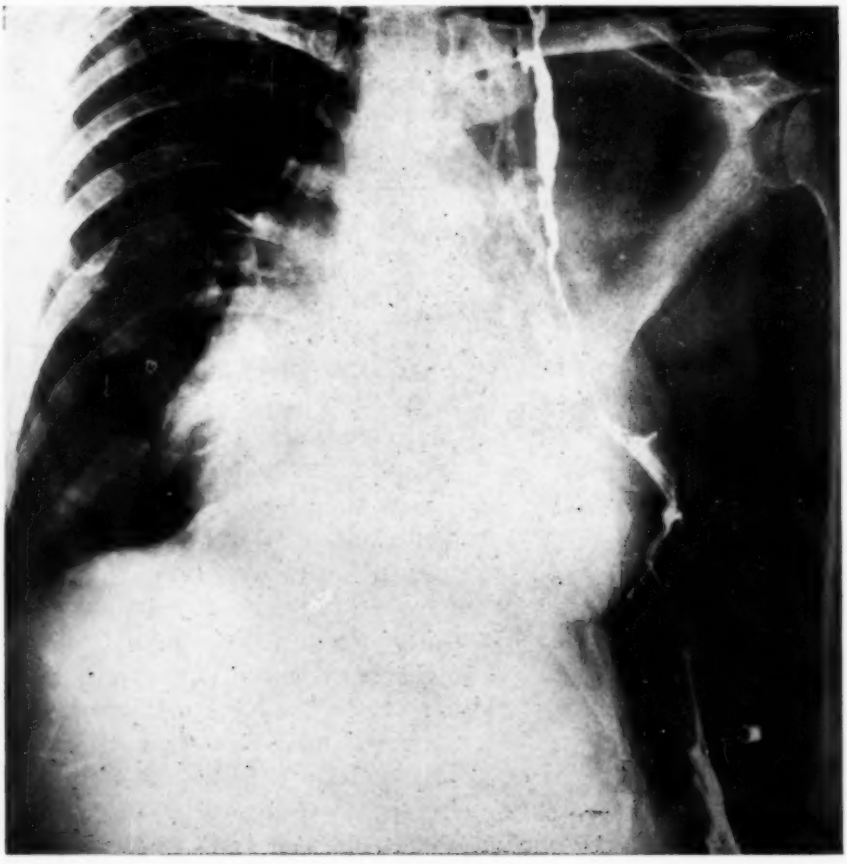

FIGURE 1: The tuberculous sinuses noted above have been closed for over eighteen months following topical treatment with penicillin and streptomycin dissolved in a germicidal detergent solvent.

that was removed failed to establish a diagnosis of tuberculosis. Nevertheless, on the basis of the past history, 4 m.l. of a solution of streptomycin and penicillin dissolved in a detergent solvent was instilled every eight hours night and day for 8 days and the sinus promptly closed. The solution was prepared by dissolving one million units of penicillin and one million units of streptomycin in 100 m.l. of zephiran chloride aqueous solution, 1:1000. In our original antibiotic detergent solution (October 13, 1946), we used only streptomycin, whereas in March, 1948 we combined streptomycin and penicillin with the germicidal detergent solvent. The chemicals are compatible and retain or exceed the component activity of streptomycin alone or penicillin alone when tested with Staphyloccus aureus or Escherichia coli.

The lesion treated by instillation of antibiotic detergent solution deep into the tuberculous sinus represents essentially a collapsed

FIGURE 2: This picture shows all the sinuses closed after previously discharging purulent infected tuberculous material for over eight years. At various intervals there were six discharging sinuses, and when treatment was started two were present.

chronic tuberculous empyema. In the light of present trends to expand collapsed lungs by decortication, the original thoracoplasty may have been unwise. A philosophy of conservative treatment is in keeping with the recommendation to use aerosolized detergent antibiotics by inhalation as the method of choice before resorting to collapse therapy.

Previous experience in closing the draining sinuses of 35 patients suffering from chronic osteomyelitis prompted us to attack the more formidable problem of a known tuberculous sinus.

The patient was emphatically instructed from the very outset to lie constantly on her right side so that the antibiotic detergent solution would drain by gravity into the ramifications of the sinus tract located on her left side, thereby attaining maximum topical efficiency. Within four days the discharge from the sinus diminished markedly and the cavity closed completely at the end of 14 days. Now, 15 months have elapsed and the sinuses are still closed with no evidence of any inflammatory reaction following this extraordinarily simple procedure.

During the 14 years that this individual had been ill innumerable roentgenograms, blood studies, cultures, bacteriological

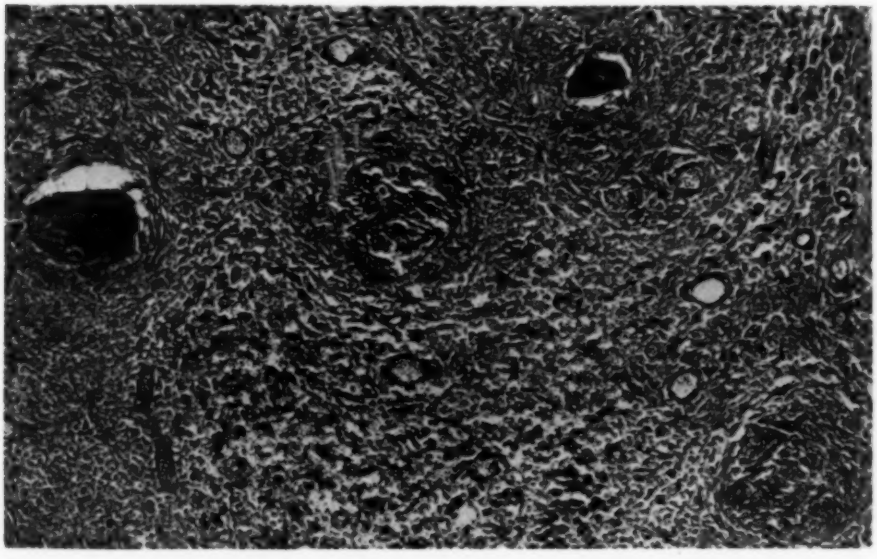

FIGURE 3: *Microscopic Examination:* The particles are composed of compact fibrous tissue surmounted by stratified, squamous epithelium along one aspect. They show focal hyperkeratosis, parakeratosis, vacuolization, atrophy and exfoliation in scattered areas. Aggregations of polyblasts are evident in portions of the corium and are scattered through the foci of the subjacent dense fibrous connective tissue. A few foci have circumscribed aggregations of epitheloid, lymphocytes, fibroblasts and multinucleated giant cells with central and peripheral distribution of nuclei. The cells are grouped in fibrillar and fibrous reticulum showing granular fragmentation. Rare acid fast rods are evident in some of the epitheloid cells after prolonged search.

Diagnosis: Chronic Inflammation; Focal Tuberculosis.

studies, and other pertinent laboratory tests confirmed the clinical picture of a chronically ill patient suffering from tuberculous empyema with sinuses. A biopsy of the visceral and parietal pleura showed both grossly and microscopically the classical pathological picture of tuberculosis. In some fields it was possible, after prolonged search, to identify acid fast rods, probably Mycobacterium tuberculosis. Following the closure of these sinuses the entire clinical and laboratory picture promptly returned to one more normal.

Realizing the irreversible damage following thoracoplasty as practiced in the pre-antibiotic era, if confronted with this problem today, thoracoplasty would not be done so promptly. Using antibiotic detergent solutions topically in the empyemic cavity, we would try to expand the lung by decortication, and by aerosol therapy attempt to eliminate the primary source of disease in the lung parenchyma, in order to effect a cure.

X-ray inspection of the chest on January 28, 1948 revealed complete thoracoplasty on the left. No evidence of active disease was seen in the right lung. The mediastinal contents had shifted to the right. The vital capacity was 33 per cent of normal. Two recent vital capacity determinations were done on different days 15 months after closure of the sinus. In spite of diminished vital capacity the patient is able to carry on with her household duties. The alteration of her blood count from one indicative of pronounced anemia to normal may be another important factor in diminishing her dyspnea.

Discussion

Considerable theoretical evidence and some factual data are now available to indicate the importance of multiple chemotherapeutic agents in forestalling the development of resistant bacterial strains. No apparent antibacterial synergism is noted in zephiran streptomycin solutions, although this quarternary ammonium germicide has a powerful potentiating effect upon penicillin under certain conditions. The treatment of infected surfaces with solutions of reduced surface tension offers the advantage of enhanced penetration. However, quarternary ammonium compounds are considerably less effective in this respect than the esters of sodium sulfosuccinate we have employed previously in the treatment of osteomyelitis.

The clinician will be primarily interested in the rapid and successful closure of the sinus tract in this patient. As a comparison the report of Hinshaw et al.[5] may be noted. Hinshaw, Feldman and Pfuetze, in reviewing 100 cases of tuberculous sinuses, report that, for satisfactory treatment, streptomycin therapy should not

be undertaken unless adequate amounts of the drug are available; that is, sufficient for a period of two to four months treatment, in which one to three grams is used daily for a total requirement of 360 grams.

Advantages of the infinitely simple method of topical therapy become obvious when we consider the severe, often irreversible, toxic damage associated with prolonged use of streptomycin. In reviewing a series of cases given streptomycin parenterally over a long period of time, McDermott and his associates noted, with some concern, the systemic damage that might follow such a procedure. The simple topical approach, using streptomycin locally in a surface active germicide limits immediately the danger of systemic tissue damage because of the relatively minute amount used. With topical treatment there is virtual elimination of streptomycin penetrating into the systemic circulation for prolonged intervals of time, with the resulting possibility of tissue damage.

In contrast to the studies of Hinshaw and those of Brock, the method of treatment we suggest is distinguished by the rapidity of response and the brevity of the therapeutic program. In terms of conserved streptomycin, reduced hospitalization time and absence of prolonged dependence on our overstrained medical facilities the method deserves a thorough exploration by physicians dealing with the disabling lesion of chronic tuberculous sinus.

SUMMARY

In chronic infected sinuses, either tuberculous or non-tuberculous, the efficiency of the treatment will increase in direct proportion to the intimacy of the contact between the antibiotic and the pathogen. Using a quarternary ammonium compound (Zephiran) as a detergent with penicillin and streptomycin in very minute amounts, we have closed permanently a chronic tuberculous sinus. We emphasize the permanency of the closure because the technique described above, using known fundamentals in genetics, decreases the development of bacterial resistant strains. The simple topical approach, because of the relatively minute amount of streptomycin used, avoids the danger of systemic tissue damage.

REFERENCES

1 Brock, B. L.: "Streptomycin in the Treatment of Draining Tuberculous Sinuses," *J.A.M.A.*, 135:147, 1947.
2 Grace, E. J. and Bryson, V.: "Non-Operative Treatment of Chronic Osteomyelitis with Penicillin and a Wetting Agent," *J.A.M.A.*, 130:741, 1946.
3 Bryson, V. and Grace, E. J.: "Aerosol Therapy of Respiratory Disease: A Report of Fifty Cases," *New Eng. J. Med.*, 237:683, 1947.
4 Grace, E. J. and Bryson, V.: "Antibiotic-detergent Aerosols and Supportive Therapy in Pulmonary Tuberculosis," *Medical Times*, 75:372, 1947.
5 Hinshaw, J. C., Feldman, W. H. and Pfuetze, K. H.: "Treatment of Tuberculosis with Streptomycin," *J.A.M.A.*, 132:778, 1946.

The Use of Dihydrostreptomycin in the Treatment of Tuberculosis*

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Although streptomycin is an invaluable drug in the treatment of certain types of tuberculosis, its neurotoxicity is a distinct disadvantage. This neurotoxicity, manifested by impaired function of the vestibular apparatus, almost always develops when a daily dose of 2 or 3 gm. is given for a period of several weeks. The incidence is markedly decreased when the daily dose is reduced to 1 gm., but it is generally believed that this dose of the drug probably is inadequate for certain types of disease such as miliary and meningeal tuberculosis. Furthermore, convincing evidence has not yet been presented showing that a daily dose of 1 gm. is as effective as twice this amount in the treatment of pulmonary tuberculosis and other less responsive types of the disease. The discovery of a new drug with the antituberculosis activity of streptomycin but with lessened neurotoxicity would be a distinct improvement, and preliminary studies suggest that dihydrostreptomycin has these characteristics.

Dihydrostreptomycin was first described in 1946 by Peck and co-workers.[1] Two other groups of workers[2,3] independently reported the preparation of this same drug shortly thereafter. This new drug was prepared by the catalytic hydrogenation of streptomycin and was found to be more stable than the parent substance.

The effect of dihydrostreptomycin on tubercle bacilli was first studied by Youmans,[4] who found that it had the same inhibitory effect as streptomycin on the growth of the H37Rv strain of tubercle bacilli in vitro. This has been confirmed by several groups[5-9] working with numerous strains of tubercle bacilli with but one exception. Rake and his associates[6] reported that they had found one strain of human tubercle bacilli for which the minimal inhibiting concentration of dihydrostreptomycin was consistently larger than that of streptomycin. The observation that streptomycin-resistant strains of tubercle bacilli are equally resistant to dihydrostreptomycin in vitro has been reported by several investigators.[7-9]

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The treatment of experimental tuberculosis in animals with dihydrostreptomycin was first reported by Freedlander and French,[10] who found dihydrostreptomycin to have the same effect as streptomycin on experimental tuberculosis in guinea pigs. This has been confirmed by Feldman and his associates[8] and these latter workers have shown that dihydrostreptomycin has no demonstrable effect on tuberculosis produced experimentally in guinea pigs by the injection of a streptomycin-resistant strain of tubercle bacilli. Rake and co-workers reported that the two drugs were equally effective against experimental tuberculosis in mice caused by the Ravenel strain of Mycobacterium tuberculosis, and Edison and her associates[7] found the same to be true of avian tuberculosis in chicks.

The neurotoxicity of streptomycin and dihydrostreptomycin was compared in an experimental study by Edison and her associates using cats and dogs. They found that dihydrostreptomycin caused much less damage to the vestibular apparatus than did streptomycin. Similar findings in cats were reported by Hobson and his co-workers.[9]

The first clinical trials of dihydrostreptomycin were reported by Tompsett.[11] He gave the drug to five patients who had reacted unfavorably to streptomycin, four with drug fever and one with asthma. All five of these were able to take dihydrostreptomycin without difficulty.

After experimental studies in animals had shown that dihydrostreptomycin was as effective as streptomycin in controlling experimental tuberculosis and that it was less neurotoxic than streptomycin, a comprehensive study of the effects of dihydrostreptomycin on patients with tuberculosis was begun independently by two groups of investigators.[9,12] Both of these groups have made preliminary reports indicating that dihydrostreptomycin apparently has the same therapeutic effectiveness as streptomycin and that it causes much less damage to the vestibular apparatus. The concentration of dihydrostreptomycin in various body fluids has been studied by Hobson and his co-workers[9] and by Levin and his co-workers,[13] and the results of both of these investigators are comparable to the results in similar studies of streptomycin. Thus the apparent difference in the neurotoxicity of the two drugs could not be explained by differences in the concentrations of the drugs in the blood serum and other body fluids.

The present report is a summary of our experience with the first 35 patients whom we treated with dihydrostreptomycin.* Both

*The dihydrostreptomycin utilized in these studies was supplied by Merck & Co., Inc., Rahway, New Jersey, through Dr. James M. Carlisle and Dr. Augustus Gibson.

the hydrochloride and the sulfate forms of the drug were used, the concentration of each being 0.2 gm. per cubic centimeter of distilled water. The drug was always given intramuscularly, the total daily dose usually being divided into injections of 1 gm. at intervals of eight to 24 hours. The pertinent data regarding the occurrence of vestibular damage of these 35 patients are given in Table 1.

Neurotoxicity

Tests of vestibular function using the quantative method of Kobrak were done on all patients before, during (usually at two-week intervals) and at the completion of treatment (except for one patient whose treatment was completed elsewhere). In addition, patients were questioned frequently regarding the occurrence of dizziness, deafness, visual disturbances and paresthesias. The infrequency of vestibular damage can be seen from the data in table 2.

Six patients have been given 3 gm. of dihydrostreptomycin per day. One patient (case 1) received the drug for only 10 days and was comatose during this time owing to tuberculosis meningitis, so that tests of vestibular function could not be performed.

The patient in case 2 had first been treated with streptomycin, 2.8 gm. per day for eight days, when symptoms of vestibular damage developed. Fourteen days later 2.0 gm. of streptomycin per day was given for three days, and again administration of the drug had to be discontinued because of vertigo. After a lapse of six weeks she was given dihydrostreptomycin in a dose of 3.2 gm. per day. After 20 days the dizziness returned and hypofunction of the labyrinths was noted. This patient had renal failure with a blood urea of 140 mg. per 100 cc. and the blood concentration of dihydrostreptomycin was found to be 320 micrograms per cubic centimeter of serum. The other four patients in this group received 3 gm. of dihydrostreptomycin per day for 38 to 60 days. In case four mild vertigo developed after 42 days of treatment and the caloric test revealed slight bilateral hypofunction of the vestibular apparatus. Administration of the drug was stopped and the symptoms subsided within a week, and a caloric test eight months later revealed improvement in labyrinthine function in both sides, the left side being normal at this time. In the last of this group (case 6) no symptoms of vestibular damage developed and the results of the caloric tests performed every two weeks during treatment remained normal until the end of treatment, when slight bilateralhypofunction was noted.

Twenty-six patients have been treated with 2 gm. of dihydrostreptomycin per day, most of them for 60 days. In only four of

TABLE 1

Data on 35 Patients Treated with Dihydrostreptomycin

Case	Age, years, and sex	Weight kg.	DAILY DOSE Gm.	Mg./kg. body weight	Injections per day	Days treated	Vestibular damage
1	39 M	?	3	?	3	10	?
2	49 F	83.2	3.2	38.5	8	20	Yes
3	56 M	?	3	?	3	38	No
4	32 M	93.2	3	32.2	3	42	Yes
5	56 F	52.7	3	56.9	3	60	No
6	30 F	47.3	3	63.4	3	60	Yes
7	52 M	90.5	2	22.1	1	42	No
8	24 F	50	2	40.0	2	9	
			2	40.0	1	36	
			1	20.0	1	15	Yes
9	44 F	58.6	2	34.1	1	49	
			1	17.1	1	11	Yes
10	33 F	42.7	2	46.8	1	60	Yes
11	46 M	78.2	2	25.6	1	60	No
12	66 F	39.5	2	50.6	2	35	No
13	33 F	55.0	2	36.4	2	44	
			1	18.2	1	7	Yes
14	21 F	49.1	1	20.4	1	22	
			2	40.7	2	42	No
15	49 M	57.3	2	34.9	2	60	No
16	30 F	73.2	2	27.3	2	60	No
17	43 M	58.2	2	34.4	2	60	No
18	33 M	77.3	2	25.9	2	60	No
19	39 M	72.7	2	27.5	2	60	No
20	30 F	55.0	2	36.4	2	60	No
21	40 F	60.0	2	33.3	2	60	No
22	56 F	55.5	2	36.0	2	60	No
23	40 M	74.5	2	26.8	2	60	No
24	75 M	51.4	2	38.9	2	60	No
25	42 M	75.5	2	26.5	2	60	No

TABLE 1 (Continued)

Case	Age, years, and sex	Weight kg.	DAILY DOSE Gm.	Mg./kg. body weight	Injections per day	Days treated	Vestibular damage
26	70 F	60.9	2	32.8	2	60	No
27	48 M	66.8	2	29.9	2	60	No
28	66 F	70.9	2	28.2	2	60	No
29	58 F	65.5	2	30.5	2	60	No
30	66 M	88.2	2	22.7	2	60	No
31	58 M	88.2	2	22.7	2	60	
			2	22.7	1	90	No
32	49 M	69.5	2	28.8	2	120	No
33	54 F	?	1	?	2	25	No
34	68 M	80.5	1	12.4	1	42	No
35	25 F	49.5	1	20.2	2	60	
			1	20.2	1	60	No

TABLE 2

Incidence of Vestibular Damage in Patients Treated with Dihydrostreptomycin

Daily dose, gm.	Patients treated	Patients with vestibular damage
3	6	3
2	26	4
1	3	0

TABLE 3

Incidence of Vestibular Damage in Patients Treated with 2 Gm. Dihydrostreptomycin per Day

Daily dose, mg./kg. body wt.	Injections per day	Patients treated	Patients with vestibular damage
Less than 30.0	1	2	0
	2	10	0
More than 30.0	1	3	3
	2	11	1

these cases has any sign or symptom of neurotoxicity developed. The patient in case 13 received 2 gm. a day in two injections for five weeks, after which right lower lobectomy was performed. The same regimen was continued postoperatively and on the forty-fourth day of treatment vertigo developed. The caloric test, which had previously been normal, then showed moderate hypofunction on the right side, the left remaining normal. The dose of dihydrostreptomycin was decreased to 1 gm. per day in one injection but the symptoms persisted and another caloric test six days later revealed further impairment of the function of the right labyrinth. Administration of the drug was discontinued altogether, and a week later the vertigo had diminished appreciably although the results of the caloric test had not changed. This patient had a functionless kidney on the left side and the serum sulfate did increase to 6.5 mg. per 100 cc. about the time when the vertigo developed. However, the results of other tests of renal function, including the urea clearance test, were normal. The blood concentration of dihydrostreptomycin after the intramuscular injection of 1 gm. of the drug was found to be 68.8 micrograms per cubic centimeter of serum after one hour and 14.9 micrograms after twelve and a half hours. Although these values are slightly higher than those reported by Levin and his co-workers after a similar injection, it is doubtful that the occurrence of vestibular damage in this patient can be attributed entirely to these concentrations of dihydrostreptomycin in the blood serum.

Another patient (case 8) was given a daily injection of 2 gm. of dihydrostreptomycin for a tuberculous draining sinus of the left lumbar area. After 45 days of treatment she noticed slight vertigo and the caloric test revealed slight hypo-activity of the labyrinths on both sides. The dose of dihydrostreptomycin was decreased to 1 gm. per day. By the end of the 60 days of treatment the vertigo was no longer present and a caloric test was reported to show bilateral normal labyrinthine function.

The patient in case 9 was also given a daily injection of 2 gm. of dihydrostreptomycin. She also noted slight vertigo after 49 days of treatment. The caloric test, the results of which had been normal before and during treatment, then revealed a decrease in function of the right labyrinth, the left remaining normal. The dose of the drug was decreased to 1 gm. per day and the vertigo diminished. However, the caloric test after a total of 60 days of treatment still revealed the same degree of decreased labyrinthine function on the right, the left side remaining unchanged.

The final patient to show any sign of vestibular damage (case 10) also received 2 gm. per day in one injection. The caloric test that was done before the treatment was started revealed a slight bilateral

decrease in the function of the labyrinths. No symptoms of vestibular damage developed and caloric tests performed every other week showed no change until the final test, which was done after the sixty days of treatment had been completed. This showed a slight further bilateral decrease in the labyrinthine function.

The frequency of neurotoxic changes in the group which was treated with 2 gm. of dihydrostreptomycin per day is summarized in table 3. Twelve of these patients received less than 30 mg. per kilogram of body weight per day and in none of these cases did any vestibular damage develop. The remaining 14 were given more than 30 mg. per kilogram of body weight per day. In 4 of these cases evidence of neurotoxicity developed. Three of the 14 patients received the total daily dose in one injection and all 3 of these sustained vestibular damage. In contrast, in only 1 patient of the 11 who got the same daily dose in two injections did such changes develop. Levin and his co-workers[13]studied the concentration of dihydrostreptomycin in the blood serum of 3 patients who had received 2 gm. of the drug in one injection and found it to vary from 119.2 to 214.4 micrograms per cubic centimeter one hour after the injection. Comparable concentrations of dihydrostreptomycin were probably present in the blood serum of this group of patients and it seems likely that the damage to the labyrinth was due to such high concentrations of the drug. For this reason we now believe that a daily dose of 2 gm. should be divided into two injections at 12-hour intervals.

Three patients have been treated with a daily injection of 1 gm. of dihydrostreptomycin without any sign or symptom of vestibular damage developing. The infrequency of neurotoxic reactions following the administration of dihydrostreptomycin is in marked contrast with our previous experience with streptomycin. A daily dose of 2 or 3 gm. of streptomycin for several weeks was almost always followed by serious damage to the vestibular apparatus, and in nearly 50 per cent of the patients who were treated with only 1 gm. per day some evidence of altered vestibular function developed. Although dihydrostreptomycin may cause similar changes, it does so infrequently and the damage is much less severe.

An occasional patient mentioned the occurrence of labial and digital tingling, but this usually subsided during treatment and was never of any serious consequence. One patient (case 10) noted that she was unable to hear her wrist watch tick for about six weeks after the completion of her treatment. However, when she was examined four months after the completion of the treatment she had no subjective deafness and an audiogram was normal. Another patient (case 15) complained of similar deafness and

an audiogram made four months after completion of his treatment revealed the development of deafness for the high tones (frequencies of 2,048 and higher). No other patient noticed any deafness and audiograms on 15 more of these patients from three to eight months after treatment did not reveal evidence of auditory damage.

Allergic Manifestations

Allergic signs and symptoms were searched for and a weekly differential blood count was performed on most of the patients. There were no allergic reactions, and one patient in whom a drug fever and an exfoliative dermatitis had developed from streptomycin was able to take dihydrostreptomycin without difficulty. At the time of our preliminary report[12] we had not observed the development of eosinophilia, but we have subsequently detected 7.5 per cent or more of eosinophils (maximum 15.5 per cent) in nine patients. However, there was no correlation between the size of the daily dose of dihydrostreptomycin and the occurrence of eosinophilia or between the eosinophilia and the manifestation of neurotoxicity.

Systemic Toxicity

Twenty-one of these patients were studied intensively to detect any sign of damage to the kidneys or the liver, the function of these organs being tested at weekly to monthly intervals. No evidence of damage to either system was detected. Complete blood counts and a determination of the concentration of hemoglobin were done at weekly intervals and no sign of damage to the hematopoietic system was observed.

In our previous report[12] we noted that two patients had complained of abdominal distress and gaseous dyspepsia which was relieved when the treatment was stopped. We have not observed this in any additional cases.

Local Irritation

We have studied the local irritation produced by numerous lots of dihydrostreptomycin, both in the form of the hydrochloride and of the sulfate. Some of the early preparations caused a tender region of induration in the muscle at the site of the injection, but recently the preparations of dihydrostreptomycin have caused no more irritation than injections of similar amounts of streptomycin.

The intrathecal injection of some of the early preparations of dihydrostreptomycin caused untoward reactions and led us to discontinue the administration of the drug by that route. Al-

though we have not had occasion to resume the intrathecal administration of dihydrostreptomycin, we believe that the present preparations of dihydrostreptomycin would be satisfactory for intrathecal administration.

Therapeutic Efficacy

Evidence has been presented showing that dihydrostreptomycin is as effective as streptomycin in inhibiting the growth of tubercle bacilli in vitro.[4-9] Likewise it has been shown that the two drugs are equally potent in suppressing experimental tuberculosis in chicks, mice and guinea pigs.[6-8,10] There has not yet been sufficient time to determine if dihydrostreptomycin is as effective as streptomycin in the treatment of various types of tuberculosis in humans, but it is our clinical impression that dihydrostreptomycin is the equal of streptomycin in this respect.

Two of the patients in the present series were treated for nontuberculous conditions and two others have been under treatment for too short a period to determine whether or not there will be a satisfactory response. Nine of these patients have far-advanced, fibrocavernous tuberculosis of the lungs which would not be expected to respond, and these patients were given dihydrostreptomycin along with promin and para-aminosalicylic acid to determine if the administration of other antituberculosis drugs along with dihydrostreptomycin would delay or prevent the emergence of dihydrostreptomycin-resistant strains of tubercle bacilli. In five patients it was impossible to study the therapeutic efficacy of dihydrostreptomycin for various reasons, such as an inadequate period of treatment or the surgical removal of the diseased portion of lung. This leaves 17 patients in whose cases the therapeutic effect of the drug could be evaluated, and we feel that these patients responded to treatment just as we would have expected them to do if they had been given streptomycin instead of dihydrostreptomycin.

The following cases are examples of responses which we have seen.

Tuberculous Sinuses

The patient in case 10 first came to the Mayo Clinic in 1918 at the age of 3 years, at which time she was found to have tuberculosis of the lumbar vertebrae. A draining sinus developed in the right groin in 1920 at the age of five years, and subsequently others developed in the left groin and one in each lumbar region. She was treated with rest and suitable braces and corsets with satisfactory control of the vertebral disease. Some of the sinuses ceased to drain for short periods, but at least one of them was discharging pus at all times from 1920 until we saw her in November, 1948. At that time the one in the left lumbar region had drained con-

tinuously for 20 years and the ones in the left groin had been open for 17 years (Fig. 1a). Treatment with dihydrostreptomycin was advised and she was given 2 gm. of the drug (46.8 mg. per kilogram of body weight) intramuscularly each morning for 60 days. She was also given 1.5 gm. of para-aminosalicylic acid* orally three times daily and 0.4 gm. of promin* once each day in an effort to delay or prevent the emergence of dihydrostreptomycin-resistant strains of tubercle bacilli.[14]

The response to this regimen of treatment was remarkable. All four of the sinuses had ceased to drain by the 18th day of treatment, and for the first time in 28 years she did not have to wear a dressing to absorb the pus. The healing continued and the openings of the sinuses were well epithelized by the 60th day (Fig. 1b). She was re-examined four months later and found to be well with the sinuses still closed.

Comment — Four other patients with tuberculous sinuses of the neck, thoracic wall, lumbar region and groin responded to treatment with dihydrostreptomycin in an equally gratifying way. These results were the equal of any that we have seen from the use of streptomycin.

Tuberculosis of the Lungs

The patient in case 6, a Negro woman aged 30 years, registered at the clinic on September 22, 1948. She complained of hoarseness of 10 months' duration. Examination of the larynx revealed an extensive ulcerating lesion characteristic of tuberculosis. Although the patient had no other symptoms, a roentgenogram of the thorax revealed caseocavernous lesions of both lungs (Fig. 2a) and those of the thoracic segment of the

*The para-aminosalicylic acid and promin utilized in these studies were supplied by Parke, Davis & Company, Detroit, Michigan, through Dr. E. A. Sharp.

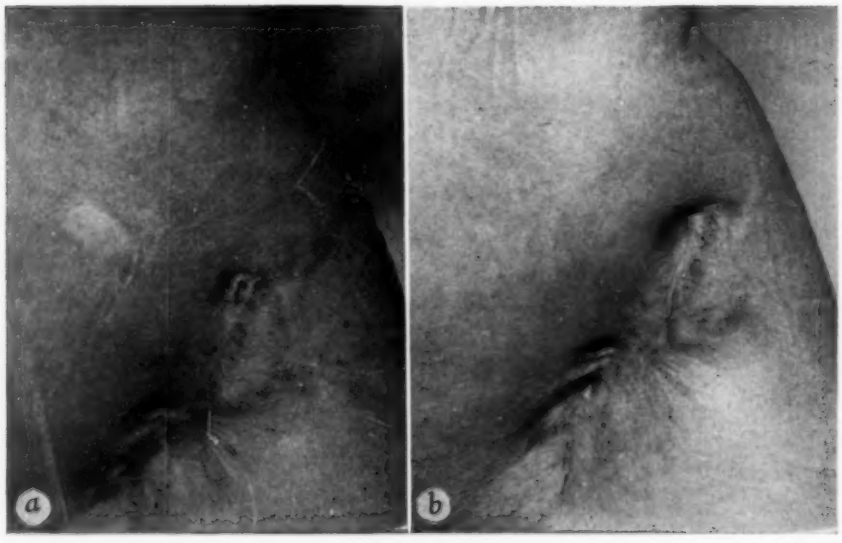

FIGURE 1: Draining sinuses in groin of patient in case 10, (a) before, and (b) after treatment.

spinal column revealed tuberculosis of the eleventh and twelfth thoracic vertebrae. A stained smear of the sputum was positive for acid-fast bacilli. She was hospitalized at once for strict rest in bed and was given 1 gm. of dihydrostreptomycin intramuscularly every eight hours (63.4 mg. per kilogram of body weight per day). A re-examination of the larynx after four weeks of treatment showed marked improvement, and after 60 days of treatment the larynx appeared to be normal except for slight thickening of the vocal cords. Serial roentgenograms of the thorax showed progressive improvement of the pulmonary lesions (Fig. 2b), and the sputum became negative for acid-fast bacilli by the concentration method. However, cultures of the sputum were still positive for acid-fast organisms. There was no demonstrable change in the appearance of the vertebral lesion during the 60 days of treatment. After this period of treatment with dihydrostreptomycin the patient transferred to a tuberculosis sanatorium in her home state for completion of her treatment.

The patient in case 11, a white man aged 43 years, was found to have active tuberculosis of the lungs with nodular and fibrotic lesions throughout both lungs in September, 1945. A stained smear of the sputum was positive for acid-fast bacilli. He entered a tuberculosis hospital where he remained for two years, during which time he was treated with rest in bed, right phrenemphraxis and pneumoperitoneum. His lesions became stable by serial roentgenograms and the sputum became negative for acid-fast bacilli. However, the cultures of the gastric washings remained positive for acid-fast bacilli. He was dismissed from the sanatorium in November, 1947, to continue rest and pneumoperitoneum therapy under

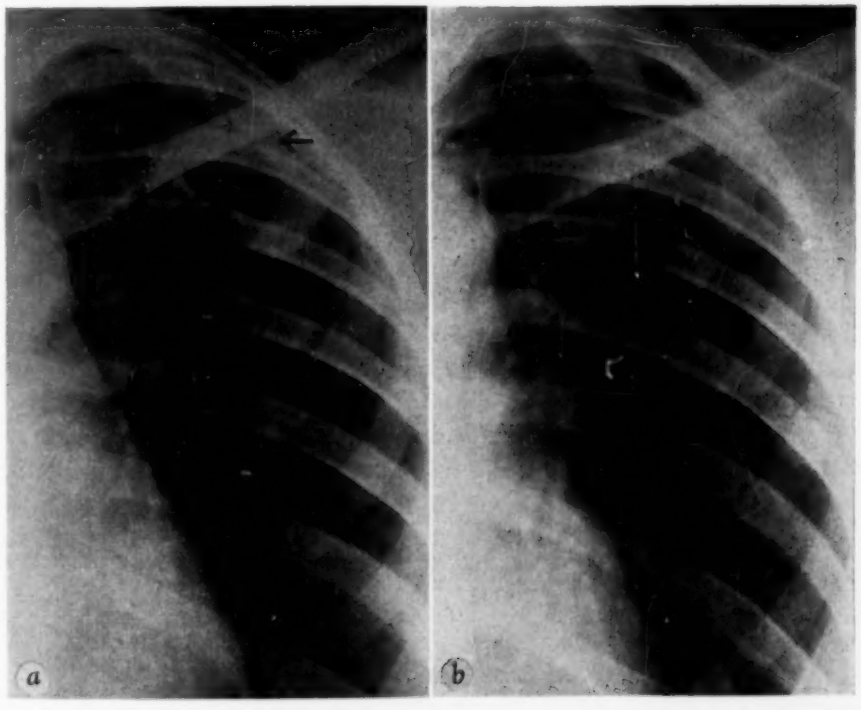

FIGURE 2a: Roentgenogram of left upper lung field of patient in case 6, showing large cavity present before treatment. (b) Same area after treatment.

our care. From then until November, 1948, there was no change in his condition; the roentgenograms of the thorax showed no change and cultures of the gastric washings were persistently positive for acid-fast bacilli. On November 6, 1948, treatment with dihydrostreptomycin was started. He was given 2 gm. (25.6 mg. per kilogram of body weight) of the drug intramuscularly once each day. He was also given para-aminosalicylic acid and promin by mouth in an effort to delay or prevent the emergence of dihydrostreptomycin-resistant strains of tubercle bacilli.[14] The dose of para-aminosalicylic acid varied from 1.5 to 3.0 gm. three times each day and the dose of promin varied from 0.4 to 0.8 gm. once each day. The drugs were administered for 60 days, during which time the pneumoperitoneum and rest were continued as before. Serial roentgenograms of the thorax at weekly intervals showed progressive clearing of the nodular lesions, which had not changed during the previous year. Gastric washings were cultured for acid-fast bacilli every two weeks and were found to be negative. Since the end of the period of treatment gastric washings have been cultured at monthly intervals and have remained negative. Roentgenograms of the thorax, also at monthly intervals, have shown no further change in the pulmonary lesions.

Comment: The responses of these two patients, one with acute exudative tuberculosis and the other with chronic nodular tuberculosis of the lungs, are examples of the results that we have seen from the use of dihydrostreptomycin in pulmonary tuberculosis. In our opinion the therapeutic results were the same as would have been obtained if equal amounts of streptomycin had been given.

Dihydrostreptomycin Resistance

The introduction of dihydrostreptomycin has not solved the problem of drug-resistant variants of tubercle bacilli. As mentioned previously, tubercle bacilli which are resistant to streptomycin are equally resistant to dihydrostreptomycin. It has also been shown that experimental tuberculosis in guinea pigs due to inoculation of streptomycin-resistant tubercle bacilli does not respond to treatment with dihydrostreptomycin.[8]

Sufficient data have not yet been accumulated to determine the rapidity or frequency with which dihydrostreptomycin-resistant strains of tubercle bacilli occur during treatment with that drug. However, it seems likely that they would occur with about the same frequency as drug-resistant variants have been found during treatment with streptomycin. Hobson and his associates[9] reported that this was true in the series of cases that they studied.

Since most of our patients treated with dihydrostreptomycin alone did not continue to discharge tubercle bacilli after treatment, dihydrostreptomycin sensitivity tests could not be carried out. However, one patient whose organisms were sensitive to 10 micrograms of dihydrostreptomycin per milliliter of culture medium before treatment was found to have micro-organisms resistant to 100 micrograms of dihydrostreptomycin per milliliter of culture medium

after 18 days' treatment with 3 gm. of the drug per day. Another patient who was treated with the same dose of the drug was found to have equally resistant tubercle bacilli after 42 days of treatment. A third patient who received 1 gm. of dihydrostreptomycin per day was found to have a resistant strain of tubercle bacilli after the completion of 42 days of therapy.

From these limited data it seems probable that dihydrostreptomycin-resistant strains of tubercle bacilli will be as great a problem as streptomycin-resistant strains have been in the past. For this reason the drug should not be used in the treatment of patients who have manifestations of tuberculosis which are known to respond well to rest and collapse therapy. When the drug is needed, its use should be carefully integrated into the over-all plan of therapy so that a maximal antituberculosis effect will be available when it is most needed.

SUMMARY

Dihydrostreptomycin, a derivative of streptomycin, has been reported to be as effective as the parent drug against the tubercle bacillus in vitro and against experimental tuberculosis in various animals. The neurotoxicity of the two drugs has also been studied experimentally and dihydrostreptomycin has been reported to be less toxic than streptomycin.

The present report summarizes our experience with the first 35 patients whom we treated with the new drug. Dihydrostreptomycin was found to be less neurotoxic than streptomycin, only four of 26 patients showing any sign or symptom of vestibular damage when a daily dose of 2 gm. was given for long periods. Two patients noted slight deafness after treatment was completed and audiograms revealed the development of deafness for the high frequencies in one of them. No allergic reactions occurred, although nine of these 35 patients had 7.5 per cent or more of eosinophils. No other changes in the blood were noted. Studies of function of liver and kidneys did not reveal damage to these organs. Dihydrostreptomycin seemed to be as effective as streptomycin in the treatment of various types of tuberculosis, but much more work must be done to determine if the same doses of the two drugs are equally effective. The frequency of dihydrostreptomycin-resistant strains of tubercle bacilli is not yet known, but three of these patients discharged resistant organisms during treatment, one of them after only 18 days of therapy.

RESUMEN

La dihidroestreptomicina, derivado de la estreptomicina, se ha encontrado tan efectiva contra el bacilo tuberculoso como la droga

pariente, tanto in vitro como en la tuberculosis experimental en diversos animales. La neurotoxicidad de las dos drogas se ha estudiado también experimentalmente y la dihidroestreptomicina se ha encontrado menos tóxica.

La presente comunicación resume nuestra experiencia con los primeros 35 enfermos tratados con la nueva droga. La dihidroestreptomicina se ha encontrado menos nuerotóxica que la estreptomicina; solo 4 de 26 enfermos mostraron algún signo de daño vestibular cuando se dió una dósis diaria de 2 gms. por largos periodos. Dos enfermos notaron ligera sordera después de terminado el tratamiento y los audiogramas demostraron el desarrollo de sordera para las altas frecuencias en uno de ellos.

No ocurrieron reacciones alérgicas aunque 9 de 35 enfermos tuvieron 7.5 por ciento o más de eosinófilos. No se encontraron otros cambios en la sangre. El estudio de las funciones hepática y renal no reveló daño alguno a estos órganos. La dihidroestreptomicina pareció tan efectiva como la estreptomicina en el tratamiento de varias formas de tuberculosis, pero se requiere mucho trabajo en adelante para determinar si las mismas dosis de las dos drogas son igualmente efectivas. La frecuencia de las cepas dihidroestreptomicino-resistentes no es aún conocida, pero tres de los enfermos eliminaron bacilos resistentes durante el tratamiento; uno de ellos apenas después de 18 días de tratamiento.

REFERENCES

1 Peck, R. L., Hoffhine, C. E. Jr. and Folkers, Karl: "Streptomyces Antibiotics: IX. Dihydrostreptomycin," *J. Am. Chem. Soc.*, 68:1390, 1946.

2 Bartz, Q. R., Controulis, John, Crooks, H. M. Jr. and Rebstock, Mildred C.: "Dihydrostreptomycin," *J. Am. Chem. Soc.*, 68:2163, 1946.

3 Fried, J. and Wintersteiner, O.: "Streptomycin: II. Reduction and Oxidation Products of Streptomycin and Streptobiosamine," *J. Am. Chem. Soc.*, 69:79, 1947.

4 Youmans, G. P.: Quoted by Bartz, Q. R., Controulis, John, Crooks, H. M. Jr. and Rebstock, Mildred C.[2]

5 Donovick, Richard and Rake, Geoffrey: "Studies on Some Biological Aspects of Dihydrostreptomycin," *J. Bact.*, 53:205, 1947.

6 Rake, Geoffrey, Pansy, F. E., Jambor, W. P. and Donovick, Richard: "Further Studies on the Dihydrostreptomycins," *Am. Rev. Tuberc.*, 58: 479, 1948.

7 Edison, A. O., Frost, B. M., Graessle, O. E., Hawkins, J. E. Jr., Kuna, S., Mushett, C. W., Silber, R. H. and Solotorovsky, M.: "An Experimental Evaluation of Dihydrostreptomycin," *Am. Rev. Tuberc.*, 58:487, 1948.

8 Feldman, W. H., Karlson, A. G. and Hinshaw, H. C.: "Dihydrostreptomycin: Its Effect on Experimental Tuberculosis," *Am. Rev. Tuberc.*, 58:494, 1948.

9 Hobson, L. B., Tompsett, Ralph, Muschenheim, Carl and McDermott, Walsh: "A Laboratory and Clinical Investigation of Dihydrostreptomycin," *Am. Rev. Tuberc.*, 58:501, 1948.

10 Freedlander, B. L. and French, F. A.: "Dihydrostreptomycin in Experimental Tuberculosis: A Preliminary Report," *Dis. of Chest*, 13: 708, 1947.

11 Tompsett, Ralph: "Relation of Dosage to Streptomycin Toxicity," *Ann. Otol., Rhin. and Laryng.*, 57:181, 1948.

12 Hinshaw, H. C., Feldman, W. H., Carr, D. T. and Brown, H. A.: "The Clinical Administration of Dihydrostreptomycin in Tuberculosis: A Preliminary Report," *Am. Rev. Tuberc.*, 58:525, 1948.

13 Levin, Louis, Carr, D. T. and Heilman, F. R.: "The Distribution of Dihydrostreptomycin in Various Body Fluids," *Am. Rev. Tuberc.*, 58: 531, 1948.
14 Karlson, A. G., Pfuetze, K. H., Carr, D. T., Feldman, W. H. and Hinshaw, H. C.: "The Effect of Combined Therapy with Streptomycin, Para-aminosalicylic Acid and Promin on the Emergence of Streptomycin-resistant Strains of Tubercle Bacilli: A Preliminary Report," *Proc. Staff Meet., Mayo Clin.*, 24:85, 1949.

Discussion

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In discussing Dr. Carr's paper I shall limit myself to the clinical aspects of the "Case of Dihydrostreptomycin," since this new drug has not been the answer to the drug resistance bug-a-boo which has so handicapped us with the older drug streptomycin. As Dr. Carr has pointed out, resistance to the one connotes resistance to the other.

In many respects I am in complete agreement with the Mayo group's conclusions concerning the toxicity of dihydrostreptomycin but there are one or two differences in our thoughts which concerns first the neurotoxicity, and second the therapeutic efficacy of the drug.

You have learned from Dr. Carr's paper that 35 patients were treated with 1 to 3 grams of the drug daily for periods ranging from eight to 150 days. In analyzing these treatment periods it will be seen that one patient was treated 150 days, one 120 days, one 64 days, 24 60 days, one 51 days, and seven 42 days or less. In other words 32 patients of the group of 35 were treated for 60 days or less. I believe that this fact accounts entirely for the discrepancies in neurotoxic manifestations in the Mayo group and in our group treated at Rutland Heights. We treated 20 patients with daily dosage of 2 to 3 grams, 2 grams in 10 cases and 3 in 10, for a period of 90 days with one exception, the case of a man of 24 years of age who had vestibular loss on the 60th day of treatment (daily dose of 3 grams) at which time the drug was discontinued.

Reviewing the toxic manifestations we have observed we are in agreement with the observations made by Dr. Carr and his coworkers except as regards neurotoxicity and more specifically as regards involvement of the cochlear nerve.

We have observed no allergic skin reactions either in the patients being treated or in the nurses giving the injections. Rashes, so common in streptomycin treated cases, were not observed. There were no cases of drug fever. We had six patients (30 per cent)

who showed an eosinophilia which ranged between 5 and 8 per cent. This is a little above the upper limit of normal and in sharp contrast to the eosinophilias of 15 and 20 per cent so commonly observed in the streptomycin treated cases.

Except for an early drop in red counts in nine patients (45 per cent) which soon returned to normal in spite of continued treatment and which is probably without much significance, there was no apparent damage to the hematopoietic system.

There was no conclusive evidence of renal or liver damage, the function of these organs being tested at various intervals. Two patients had slight nausea early in treatment which was not very impressive and no dose of the drug was omitted because of it.

Concerning local irritability of the drug, all patients complained of burning pain immediately after injections and soreness at the site of injections when the early lots of the drug were used. At that time we were using the dihydrostreptomycin hydrochloride "Merck". This was much more marked than in the case of streptomycin. With subsequent lots which presumably were more purified, however, we had less complaints from the patients who at first were almost on the verge of mutiny. I believe that I was the first to use the new sulfate which Dr. Carlisle of the Merck Company sent me to try on our group. Testing the entire group of 20 patients with injections of the sulfate in their left arms and an equal amount of the hydrochloride in their right 19 patients complained of pain in their right or hydrochloride arm and none in their left or sulfate arm, the exception being a man in complete euphoria who had no pain in either.

Concerning vestibular damage we had only one patient who demonstrated any substantial degree of vestibular involvement as determined by the Kobrak test. I mentioned him before.

Four patients of our group (20 per cent) developed definite evidence of cochlear nerve involvement which was revealed both clinically and audiometrically. Strange to say these changes did not appear until after completion of the 90 days course, with one exception; the man who lost vestibular function. He developed some tinnitus toward the end of his second month of treatment and an audiogram taken on his 60th day revealed some loss in the high tones. Subsequent audiograms in this patient revealed further hearing loss and his tinnitus continued for a few weeks but now, six months later it has disappeared. He has no dizziness or ataxia of any degree now but his vestibular function has not returned.

The second patient who showed some cochlear nerve involvement, the only one who was receiving 2 grams daily in the group of four who showed evidences of neurotoxicity, was a 52 year old

white male who complained of tinnitus one month after completing his 90 day course. An audiogram at this time revealed some loss in the higher tones. His tinnitus has persisted to the present, three months post-treatment. He has no clinical deafness. Concomitantly with his tinnitus he complained of occasional staggering, especially in the dark, and loss of balance when bending over. The Kobrak test did not reveal vestibular loss.

The third patient, a man of 30, revealed no evidence of cochlear nerve involvement until two months post-treatment when he developed tinnitus and some deafness. His audiogram for the first time revealed some loss of function.

The fourth patient, a man 37 years of age had no symptoms until one month following the completion of his 90 day course. At this time he had tinnitus and mild deafness, both of which increased markedly in severity up to the present. Audiograms taken at the onset of tinnitus revealed hearing loss and subsequent audiograms have been worse.

In addition to these four patients in our group of 20, who developed cochlear nerve involvement, I wish to mention another, that of a negro in his early twenties who was admitted to Rutland with acute generalized miliary tuberculosis without evidence of meningitis. He had been given two months of dihydrostreptomycin in a dosage of 3 grams daily at another hospital prior to admission. Because of our miliary protocol we switched to streptomycin in a dosage of 2 grams daily. At the end of one month of such treatment he complained of tinnitus and deafness and an audiogram revealed considerable loss of function. His deafness rapidly became worse until he was completely deaf. Since in treating well over 300 cases with streptomycin in dosage from 1 to 3 grams daily for periods ranging from 42 to 150 days, we had no evidence of deafness and no audiometric changes of any degree, we believe that this patient's deafness was due to the two months of dihydrostreptomycin he received before he came to us rather than to the streptomycin he received from us for a month.

The fact that we are observing cochlear nerve involvement in dihydrostreptomycin treated cases alters our earlier impression that this drug was relatively non-toxic.

I cannot entirely subscribe to Dr. Carr's impression that therapeutically dihydrostreptomycin is as effective gram for gram as streptomycin. In reviewing our roentgenograms we concluded that only 65 per cent had shown improvement and then the improvement was mostly slight or at most moderate. This is at variance with our streptomycin groups who demonstrated improvement between 80 and 90 per cent and then at times to marked degree. However, in such a small series it would be foolish to base too

much on these figures. Hundreds of cases must be studied before any true conclusions concerning the superiority of one of these drugs over the other can be determined.

In conclusion, then, it would seem that in most respects dihydrostreptomycin was less toxic than streptomycin but in regard to neurotoxicity directed against the cochlear nerve the reverse is true. It seems quite probable that we have delayed vestibular damage by the hydrogenation of streptomycin to form dihydrostreptomycin but at the expense of hastening or increasing damage to the cochlear nerve.

Except for further careful study with dihydrostreptomycin, which should be carried out, I should recommend the drug therapeutically only in those cases who have demonstrated sensitivity to streptomycin and then only in a dosage below 2 grams and for periods of 60 days or less.

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Dr. Carr has presented in clear and concise form information that will be valuable to all who are treating tuberculosis. There have been and are many methods of administering streptomycin as to dosage an dtime interval between doses, but it is apparent that the large doses given in the earlier use of this drug are definitely tapering off. Invariably when large doses of streptomycin sulfate were used, vestibular damage began to show up anywhere from one week on, and in many cases, it was necessary to discontinue the treatment due to increasing symptomatology affecting the vestibular system.

At that time we were not doing sensitivity tests with streptomycin and no doubt resistant strains of tubercle bacilli often developed, making useless any further treatment at that time. However, we were proceeding on the empirical formula of giving it from three to four months in large doses.

One case of tuberculous meningitis was treated with streptomycin sulfate in the dosage of 3 gm. daily and 200 mg. daily intrathecally for 123 days. At the end of 10 weeks of streptomycin sulfate therapy, there was little if any improvement. Tubercle bacilli were still present in the spinal fluid and it was then that streptomycin dihydrochloride became available and we changed to that form. Immediate improvement was noted, and at the end of 123 consecutive days of streptomycin, treatment was discontinued as her temperature and spinal fluid were normal and she was developing some local reaction from the intrathecal injec-

tions. After two years, the patient is alive and well although she is totally deaf, and this damage started early in the treatment of the tuberculous meningitis. However, we decided that it was better to have a deaf person and living, so we continued treatment irrespective of the vestibular damage. She was also extremely dizzy during treatment. Apparently this person did not develop a resistant strain of tubercle bacilli as improvement started 10 weeks after treatment was started.

Another patient treated for three monthe following the removal of a tuberculous kidney received 1.5 gm. daily for 85 days and was not tested for resistant strains of tubercle bacilli. The only reaction he developed was disturbance of equilibrium which persists one year later. His hearing is not at all diminished but his equilibrium does not function when he leans forward as he is liable to keep on falling.

Pulmonary cases treated with streptomycin in the 3 gm. dosage invariably developed symptoms affecting the vestibular system and also various other manifestations such as skin and gastrointestinal reactions. In these cases where vestibular damage or any other reaction was beginning to show, symptomatology, streptomycin was discontinued and in most cases, with the exception of the two above noted, the damage disappeared to a great extent.

When dihydrostreptomycin became available, it was used in the dosage of 1 to 1.5 gm. daily in two equally divided doses and 39 cases have been treated and are under treatment with this preparation. One case in particular who could not take streptomycin sulfate without developing a severe allergic reaction in the form of an intense irritation of the skin and a severe swelling of the face, was started on dihydrostreptomycin in the dosage of 0.1 gm. daily for one week to determine if dihydrostreptomycin could be taken without reaction. No reaction occurring, the dosage was increased to 1 gm. daily and no reaction developed. This has been the experience of many in our cases.

Two cases, one bilateral far advanced, exudative in type, and one with a bronchopneumonic spread to the contralateral lung showed dramatic improvement in one month and the sputum converted in the first case in four weeks and in the second case in six weeks.

After our initial period of using large doses of streptomycin sulfate and the dihydrostreptomycin and the calcium chloride complex, we decreased the dosage of these preparations to 1.5 gm. or 1 gm. and the reactions were less in number and less severe; and in practically all cases when the drug was withdrawn the damage disappeared to a great extent.

In November 1948, we started using dihydrostreptomycin in the

dosage of 1 to 1.5 gm. (mostly 1 gm.) in two equally divided doses and in no case have we given over 1.5 gm. Following this regime, all the reactions noted were slight dizziness in two cases and impaired hearing in one. These symptoms disappeared when the dihydrostreptomycin was discontinued. Therefore as dihydrostreptomycin was not given in large dosage, we have no way of comparing the reactions which might have occurred with dihydrostreptomycin in the same dosage as streptomycin sulfate.

When dihydrostreptomycin was started, we also began making sensitivity tests so as to ascertain if resistant strains of tubercle bacilli were developing and in about 40 per cent of the 39 cases, treatment was discontinued as a resistant strain was developing to such an extent that the drug was not of further use, and some cases were discontinued as treatment did not seem to be of value. In our experience when a resistant strain of tubercle bacilli developed early in the treatment, it increased rapidly; and after two or three months of no therapy the resistant strain remained and we could not again use dihydrostreptomycin.

As to local reactions, dihydrostreptomycin did not cause so many or so severe ones as streptomycin.

In laryngeal tuberculosis we have obtained excellent results insofar as the laryngitis is concerned with the dosage of 0.2 gm. daily. Many of these cases were far advanced terminal cases and it was given with the one idea of making the patient comfortable and able to eat. Without exception we were able to accomplish this in these cases. One case before admittance had a biopsy taken from the epiglottis leaving a large punched out hole with severe swelling of the surrounding tissues. Dihydrostreptomycin was immediately started in 1 gm. dosage and the surrounding edema and infiltration subsided rapidly and she was able to swallow and the pulmonary tuberculosis soon became inactive.

In the treatment of tuberculous sinuses, we have had excellent results in two cases. Both of them were of long standing but they immediately began to improve under treatment with dihydrostreptomycin. In the treatment of pulmonary tuberculosis, our cases were not too carefully selected and our results consequently were not of the best.

In resistant cases, we are now starting to use PAS but it has not been employed for a sufficient length of time to determine if it will reduce the resistant strain of tubercle bacilli or whether it will be efficacious if given alone. However, we are becoming more cautious in the use of dihydrostreptomycin and in many cases are reserving it for an emergency or when we think surgery will be necessary. We have started using dihydrostreptomycin in 2 gm. doses given at one time every two days.

I am in agreement with Dr. Carr that dihydrostreptomycin should not be used in the treatment of pulmonary tuberculosis when we think there is a reasonable chance for the disease to become arrested with bed rest and collapse therapy; and I do not think that the drug should be used indiscriminately in all cases of tuberculosis.

Antibiotics in Non-Tuberculous Pulmonary Diseases*

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The introduction of antibiotics has revolutionized the treatment of pulmonary disease. With the rapid discovery of new antibiotics, an increasing number of inflammatory lung lesions is rapidly being brought under control. It is proposed in this paper to describe the practical use of the antibiotics in non-tuberculous diseases of the chest. The useful antibiotics will be discussed in detail and some of the newer ones mentioned. The treatment of the following pulmonary diseases will be considered: Pneumonia, lung abscess, bronchitis, bronchiectasis and empyema.

Up to the present time over 100 antibiotics have been isolated, but only a few of these have practical value in the treatment of pulmonary disease. Many others will unquestionably be added as refinements in preparation and means of overcoming toxicity are discovered. At this writing, four of the antibiotics are available for treatment of pulmonary diseases, penicillin, streptomycin, aureomycin and chloromycetin.

1. *Antibiotics Useful in Pulmonary Diseases*

Penicillin: Penicillin is derived from the common mold, Penicillin notatum. It was first discovered by Fleming[1,2] in 1928. The most widely used preparation is crystalline penicillin G. readily soluble in water. It is the drug of choice in pulmonary infections caused by the following organisms: 1) Diplococcus Pneumoniae, 2) Streptococcus, 3) Staphylococcus, 4) Actinomyces Bovis, and 5) Spirochaetes.

The drug is non-toxic except for the occasional allergic reactions of dermatitis, urticaria and fever which can be readily controlled with anti-histaminics or by changing the brand of penicillin. Resistance rarely develops following penicillin therapy.

The best method of administration is by the intramuscular route, using 50,000 units of the sodium or potassium salt of penicillin G in aqueous solution every three hours around the clock. This produces quick and adequate plasma concentrations of penicillin. The dosage may be increased to 100,000 units or decreased to 25,000 units depending on the severity or mildness of the infection. Pro-

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caine penicillin G is a salt that is relatively insoluble in water and releases penicillin slowly following an intramuscular injection. A single injection of 300,000 units of procaine penicillin gives an adequate blood level for at least 12 to 24 hours, so that two such injections 12 hours apart would be adequate for most infections. The addition of 100,000 units of sodium or potassium penicillin G to the procaine penicillin provides both rapid and prolonged action up to 24 hours. When repeated injections of crystalline penicillin are not feasible, as in home therapy, the longer acting procaine penicillin should be used. Oral penicillin of the sodium or potassium salt of crystalline penicillin may be used when the parenteral method is impossible. However, five times the estimated parenteral dose must be prescribed. While the oral method has received adequate trial with considerable success, it should never be the route of choice in a severe infection.

The inhalation of vaporized solutions of penicillin is of considerable value in the treatment of broncho-pulmonary disease. From 25,000 to 50,000 units of penicillin dissolved in 1 cc. of physiological saline solution are inhaled three to five times daily by means of a vaponefrin nebulizer, preferably attached to an oxygen tank by rubber tubing. Green[3] suggests the use of Laboratory aerosol in the dilutions, and at times epinephrine and pyribenzamine solution. He states that with these solutions, local reactions to penicillin in the nose and throat are eradicated.

Intratracheal solutions of penicillin may be used and have been found to be of value where the drug is indicated. For this, 50,000 units are dissolved in 3 cc. of physiological saline and introduced with a catheter. Penicillin may also be combined with lipiodol, 1,500 units to 1 cc. of oil, and introduced as in ordinary bronchography.

Streptomycin: Streptomycin was first described by Schatz, Bugie and Waksman[4] in 1944. It is derived from certain strains of Actinomyces griseus. It is prepared in powder form, readily soluble in water or saline. The chief value of streptomycin lies in its potency against many gram-negative organisms resistant to penicillin. It is the drug of choice in the following infections involving the lungs, either primarily or secondarily: 1) Klebsiella pneumoniae (Friedlander's bacillus), 2) Pasteurella tularensis, 3) Pasteurella pestis, 4) Haemophilus influenzae, 5) E. Coli, 6) Bacillus Pyocyaneus, 7) Brucella species (with sulfonamides).

Streptomycin is more toxic than penicillin, particularly if given over a long period of time. Allergic reactions such as fever and urticaria are usually not severe and can be controlled with antihistaminics. When the drug is given in large doses longer than three weeks, involvement of the eighth nerve may take place caus-

ing vertigo, tinnitus and deafness. Even the severe cases of vertigo however, eventually compensate in spite of irreparable damage to the vestibular system. Resistance develops in the majority of cases if the drug is used a long time, starting approximately five weeks after beginning of streptomycin therapy.

The best method of administration is the intermittent intramuscular one. For the average infection, 0.5 gram every 6 hours around the clock is sufficient. As much as 4 grams daily may be necessary in severe infections.

Aerosol streptomycin is of value in infections due to gram-negative organisms. The method is the same one described in aerosol penicillin therapy, using 50,000 units of the drug dissolved in 1 cc. of physiological saline solution and repeated three to five times daily. Direct instillation into the trachea may also be used as described above.

Aureomycin: Aureomycin was isolated by Duggar[5] in 1948 from Streptomyces aureofaciens. It is a yellow crystalline powder, soluble in water and contains nonionic chlorine. It is the drug of choice in the following pulmonary infections: 1) Primary atypical (viral) pneumonia. 2) Ornithosis and Psittacosis. 3) Rickettsiae Species. 4) Salmonellae Species. 5) Bacterial pneumonia (pneumococcal, streptococcal, staphylococcal and hemophilus influenza infections, particularly if penicillin and streptomycin have failed). 6) Pasteurella Tularensis. 7) Brucella Species. 8) Endameba Histolytica.

Aureomycin is non-toxic, the only disturbing effects being occasional nausea, vomiting and diarrhea. Aluminum hydroxide offsets the nausea. The reactions may be due to impurities in the drug and do not usually necessitate discontinuing treatment. Development of resistance rarely occurs with aureomycin.

Oral dosage is the best method of administration. One gram every four to six hours for several days or until improvement occurs followed by 0.5 gram every six hours is the optimum dosage. Intramuscular therapy is usually accompanied by pain and induration at the site of injection. Intravenous therapy given in 1 per cent solution slowly may be used.

Chloromycetin: Chloromycetin was isolated by Ehrlich and Burkholder[6] from Streptomyces venezuelae in 1947 and can also be prepared synthetically. This compound contains nonionic chlorine. It is the drug of choice in the following infections which may primarily or secondarily involve the lungs: 1) Rickettsial species (especially typhus fever), 2) Ornithosis and Psittacosis, 3) Salmonella species (may be better than aureomycin), 4) Atypical pneumonia, 5) E. Coli infections, 6) Prucella species.

Chloromycetin is relatively non-toxic. It is given by mouth, starting with 1 gram dosage every four hours until clinical im-

provement occurs and later 0.5 gram every six hours. Treatment should be continued for three to five days following drop in fever.

It is noted that both aureomycin and chloromycetin have similar therapeutic effectiveness. It would appear at this time however, that aureomycin should be preferred for atypical pneumonia, the ornithosis-psitticosis group, tularemic pneumonia, Rocky Mountain spotted fever and Q fever infections. Chloromycetin appears to be more effective for typhoid, typhus and the salmonella group of infections. Both are apparently effective in brucellosis.

Some of the more promising antibiotics not yet ready for general use should be mentioned at this time.

Polymixin: Polymixin is derived from soil organism B. Polymixa. It is the most effective drug for gram-negative bacilli but is toxic to the kidney. It is more active than streptomycin against streptomycin sensitive gram-negative organisms, and is also active against streptomycin-resistant gram-negative organisms.[7]

Subtilin: Subtilin is produced by a strain of B. Subtilis. It is active against gram-positive bacteria, M. Tuberculosis, some of the fungi and E. Histolytica. It has a very low toxicity.

Bacitracin: Bacitracin is derived from strains of B. Subtilis. It is very active against gram-positive bacteria, and has been widely used in surgical infections. Its nephrotoxicity makes it unsuitable for systemic use.

Streptothricin: Streptothricin is derived from strains of Streptomyces lavendulae. It is active against fungi, but is toxic to animals.

Actidione: Actidione is produced by strains of Streptomyces griseus. It is active against yeasts and fungi, particularly Torula, but has received only limited clinical trial.

Neomycin: Neomycin is derived from Streptomyces fradiae. It is active against mycobacteria and streptomycin-resistant organisms. Its clinical value has not yet been established.

2. *Pulmonary Diseases Favorably Influenced by Antibiotic Therapy*

The most important application of the antibiotic therapy in pulmonary disease is in the treatment of pneumonia. There is now at hand a specific antibiotic for every form of pneumonia except that type due to the smaller viruses. The drug of choice and dosage is given in the following paragraphs.

Pneumonococcal Pneumonia: Penicillin is so highly specific against the pneumococcus, that it is the drug of choice in the treatment of pneumococcal pneumonia. The sulfonamides are relegated to second choice because of their potential toxicity and somewhat lesser potency. Penicillin is best administered by three

hourly intramuscular injections of 50,000 units of crystalline penicillin. Therapy should be maintained for five to seven days after the crisis. Intramuscular administration of 300,000 units of aqueous penicillin or procaine penicillin G. at 12 hour intervals give just as good results. It is likely that much smaller doses would be adequate in the average case of pneumonia, but it would be unwise to chance inadequate therapy.

Streptococcal Pneumonia: Penicillin is highly effective in the treatment of streptococcal pneumonia. Treatment should be intensive and the doses of penicillin high.

Staphylococcal Pneumonia: Penicillin is the drug of choice in staphylococcal pneumonia. Large doses should be used. Aureomycin may be of value in those cases in which the organisms have been found to be penicillin-resistant. Children with staphylococcal infections associated with pancreatic fibrosis who did not respond to penicillin were markedly benefited by aureomycin.[9]

Friedlander's Pneumonia: Friedlander's bacillus is sensitive to streptomycin and should be used in all cases. The dose should be large at the onset, usually 4 gms. daily, 1 gm. given intramuscularly at six hour intervals. The dose should be cut down to 2 gms. daily as soon as a therapeutic effect is obtained.

Hemophilus Influenzae Pneumonia: Pneumonia due to hemophilus influenzae responds promptly to streptomycin. Two to 4 gms. of the drug are given daily for approximately 10 days. Aureomycin has been found to be effective in infections due to hemophilus influenzae and should be used if streptomycin fails.

Viral Pneumonia: The pneumonias due to filtrable viruses may be classified into primary atypical pneumonias of unknown etiology and viral pneumonias of known etiology. In the latter group are included: 1) Influenzal pneumonia, 2) Ornithotic pneumonia, the best known example being psittacosis, 3) Rickettsial pneumonias comprising typhus, Rocky Mountain spotted fever and Q fever.

Aureomycin and chloromycetin are the first drugs known to be effective against any of the viral pneumonias. Aureomycin is apparently specific in the treatment of primary atypical pneumonia, ornithotic pneumonia and the Rickettsial diseases, especially Rocky Mountain spotted fever and Q fever. Chloromycetin has a similar effect and is thought to be preferable in typhus infections. So far as is known, none of the antibiotics have any influence on influenzal pneumonia. The dosage of both aureomycin and chloromycetin has been previously given.

Pneumonia Associated with Specific Infections:

Tularemia: Streptomycin is specific in its effect on tularemic pneumonia. The dosage is 2 gms. daily for approximately a week.

The result is dramatic within two to three days after the start of therapy. Aureomycin also has a favorable effect on the course of tularemia. In view of the striking results with streptomycin and greater general experience with the drug, the latter should still be the drug of choice.

Brucellosis: Pulmonary infections are rare complications of brucellosis. Aureomycin and chloromycetin are equally effective in the treatment of brucellosis, both appearing to be better than the previously used combination of streptomycin and sulfadiazene.

Pulmonary Infections due to Fungi: Several antibiotics are effective against the fungi, being both fungistatic and fungicidal in vitro. Most of them are still in the experimental stage, being too toxic for use in man. It is quite likely that some of these antibiotics will soon be available.

Penicillin is said to be valuable in the treatment of actinomycosis[10] and streptothricosis.[11] It should be used along with the other well established measures in combating fungus infections. Dosage should be large and continued for several weeks.

Actidione has been used in cryptococcosis with apparently favorable results.

Up to this time, there have been no favorable clinical reports on the use of antibiotics in histoplasmosis, coccidiomycosis or any of the other fungi.

Pneumonia of Unknown Etiology

It may frequently be impossible to determine the exact cause of a pneumonic process, particularly early in the course of the disease. This often applies to the patient who for one reason or another is unable to get hospital care, or in whom adequate laboratory tests may not be possible. Even in a modern hospital, early differential diagnosis between such diseases as viral pneumonia, coccal pneumonia, Friedlander's pneumonia and tularemia may be difficult at the onset. To wait for bacteriological confirmation or to put too much faith in the height of a white count may lose valuable time. This is particularly true in Friedlander's and tularemic pneumonia. In any seriously ill patient therefore, it is advisable to start at once with both penicillin and streptomycin, and if no improvement takes place within a short time, aureomycin and/or chloromycetin should be added. Indiscriminate use of the antibiotics should naturally be deplored as there may be development of sensitization phenomena and resistant organisms. However, when there is serious unknown pulmonary disease present, combined antibiotic therapy is indicated until the exact diagnosis can be made. In this connection, it should be stated that following the use of penicillin in pulmonary infections, penicillin-resistant

organisms, chiefly gram-negative bacilli may grow and produce disease after penicillin-sensitive organisms have been controlled.[12] This situation would necessitate the use of streptomycin, providing bacteriological evidence of new infections is found.

Diseases of the Bronchi

The antibiotics are of considerable importance in inflammatory diseases of the bronchi. In acute or chronic bronchitis which does not respond to the usual measures, a course of antibiotics should be given, particularly if sensitive organisms are found. Penicillin and streptomycin are the drugs of choice. These are best used by the aerosol method, and in severe infections, particularly in the presence of fever, supplementary parenteral therapy should be added.

In bronchiectasis, penicillin and/or streptomycin should be used for acute exacerbations, secondary pneumonia and in preparation for lung surgery. Both aerosol and parenteral methods of administration are effective. The drugs do not cure the disease, but the amount of expectoration can be considerably reduced, and often may be changed from purulent to a thin mucoid sputum. Periodic courses of antibiotics should be given depending on the character of the sputum.

Lung Abscess

Every case of lung abscess should have a thorough trial with antibiotic therapy. Penicillin is the drug of choice when gram-positive bacteria predominate in the sputum, and streptomycin should be used for infections due to gram-negative bacteria. Large doses of penicillin or streptomycin should be used both parenterally and by the aerosol method. Direct instillation of the antibiotics into the tracheobronchial tree in conjunction with bronchoscopy may prove to be of considerable value. The best results are obtained with the acute lung abscess. In chronic pulmonary abscess, antibiotics should also be used with the other well-known methods of therapy. Prior to operation, several days of antibiotic therapy makes the convalescence much smoother.

A course of aureomycin or chloromycetin may prove to be of value in lung abscesses not improved by penicillin or streptomycin.

Empyema

The organisms most commonly found in empyema are the pneumococcus, streptococcus and staphylococcus. Penicillin is therefore the drug of choice. When gram-negative organisms are present, streptomycin should be used. All acute cases should have a short trial of repeated aspirations and instillations of penicillin. Fifty thousand units of penicillin dissolved in 50 cc. of isotonic saline

are instilled daily following aspiration of the exudate. When streptomycin is used, 500,000 units are dissolved in 50 cc. of saline. Sterile saline should be used to wash out the pleural cavity if the pus is difficult to evacuate with a needle. Parenteral therapy must be continued throughout. If the infection rapidly improves as evidenced by the character of the aspirated fluid, negative culture and general improvement of the patient, then antibiotic therapy is continued. If however, no improvement takes place within a week's time or if the exudate is thick, immediate surgical drainage should be instituted. Delay of operation may result in a thickened pleura and a non-expansile lung. The intrapleural instillation of streptokinase, a fibrimolytic substance, as suggested by Drs. Hillet and Sherry,[13] liquefies the exudate and fibrin deposits on the pleura, allowing easy removal of the purulent exudate. This procedure in combination with the antibiotics would appear to be the ideal therapy for empyema and may eventually supplant surgical drainage.

Antibiotic therapy is rapidly supplanting all forms of chemotherapy in inflammatory pulmonary disease. There is available at the present time a specific antibiotic for most pulmonary infections, except those due to the smaller viruses and the fungi. It is highly probable that in the near future, the newer antibiotics will prove to be effective against the other hitherto irremediable infections of the lungs.

SUMMARY

Penicillin, streptomycin, aureomycin and chloromycetin are all invaluable in the treatment of pulmonary infections.

Penicillin is the drug of choice in all coccal pneumonias, suppurative diseases of the lungs, bronchiectasis, spirochaetal infections and actinomycosis of the lung. It is best given by the intramuscular route, using 50,000 units of crystalline penicillin G every three hours. When repeated injections are not feasable, 12 hourly injections of 400,000 units of penicillin containing 300,000 units of procaine penicillin G and 100,000 units of sodium or potassium penicillin G should be used. In suppurative lung lesions and bronchial infections, aerosol penicillin should be added, using 50,000 units of penicillin dissolved in 1 cc. of saline solution, three times daily, preferably with an oxygen tank. In empyemas, direct daily instillation of 50,000 units of penicillin dissolved in 50 cc. saline into the pleural cavity may be curative.

Streptomycin is the drug of choice in gram-negative infections of the lung. It is highly specific for pneumonias and pulmonary infections due to Friedlander's bacillus, B. tularensis, B. pestis, hemophilus influenzae and E. coli. It is best given by intramuscular

injection of ½ gram every six hours until the infection is under control. In suppurative diseases of the lungs and bronchiectasis, aerosol streptomycin in conjunction with penicillin should be used.

Aureomycin is the drug of choice in atypical pneumonia, ornithotic pneumonia, tularemic pneumonia, Rocky Mountain spotted fever, Q fever infections and brucellosis. The drug is given orally, using 1 gram every six hours for several days, and then ½ gram every six hours. Bacterial pneumonias not responding to penicillin and streptomycin may respond to aureomycin.

Chloromycetin is the drug of choice in pulmonary infections due to typhus, salmonella group, E. coli and brucella organisms. The drug is given by mouth, using 1 gram every four to six hours until improvement takes place, then ½ gram every six hours.

Combined Therapy: In pulmonary infections of unknown etiology, it is often invaluable to use both penicillin and streptomycin at once, and if in a short time improvement does not occur, aureomycin and/or streptomycin should be added.

Other Antibiotics: Several of the newer antibiotics show great promise in the treatment of hitherto incurable lesions, such as fungus and viral infections. Most of these are still toxic to animals, but it is very likely that with further refinements in preparation, they will soon prove to be effective in a still wider range of pulmonary infections.

RESUMEN

En el tratamiento de las infecciones pulmonares la penicilina, la estreptomicina y la aureomicina son de valor inapreciable.

La penicilina es la droga de elección en todas las infecciones neumónicas por cocos, supuraciones del pulmón, bronquiectasias, infecciones por espiroquetas y actinomicosis pulmonar.

Es major darla por vía intramuscular usando 50,000 unidades de penicilina cristalina G. cada tres horas. Cuando no es posible inyectar con frecuencia puede usarse Penicilina G. potásica 100,000 unidades asociada a penicilina procaínica 300,000 unidades cada doce horas. En las lesiones supurantes y bronquiales el aerosol de penicilina usando 50,000 unidades en 1 cc. de solución fisiológica tres veces al día puede usarse mediante un tanque de oxígeno. En los empiemas la instilación directa diariamente de 50,000 unidades en 50 cc. de solución salina en la cavidad pleural puede curar.

La Estreptomicina es la droga de elección en las infecciones del pulmón por gérmenes Gram negativos. Es altamente específica para las neumonías y las infecciones pulmonares por bacilo de Friedlander, bacili tularesis, pestis, hemofilo de la influenza y E. coli. Es mejor inyectarlo intramuscular a razón de medio gramo cada seis horas hasta que la infección se domine.

En las supuraciones de los pulmones y en bronquiectasias el aerosol de estreptomicina combinado con el de penicilina deben usarse.

La aureomicina es la droga preferible en las neumonías atípicas, neumonía psitacosica, tularémica, en la fiebre de las Montañas Rocallosas, en la fiebre Q. y en la brucelosis.

La droga se usa oralmente dando un gramo cada seis horas por varios días y después medio gramo cada seis horas. Las neumonías bacterianas que no responden a penicilina y estreptomicina pueden responder a la aureomicina.

La cloromicetina es la droga preferible en la tifoidea, el grupo de salmonedas, el tifo, la brucelosis y la E. coli. Se dá por vía oral un gramo cada seis horas hasta que se presente mejoría y después medio gramo cada seis horas.

Terapéutica combinada: En las infecciones de naturaleza desconocida es a menudo útil usar tanto penicilina como estreptomycina y si después de corto tiempo no ocurre la mejoría deben usarse la aureomicina y la cloromicetina.

Otros antibióticos: Varios de los más nuevos antibióticos son prometedores en el tratamiento de lesiones hasta ahora incurables. La mayoría de estas drogas son aún tóxicas para los animales, pero es posible que su refinamiento las haga útiles en otras infecciones pulmonares.

REFERENCES

1 Fleming, A.: "The Discovery of Penicillin," *Brit. Med. Bull.*, 2: No. 1, 1944.
2 Fleming, A.: "On the Antibacterial Action of Cultures of a Penicillum," *Brit. J. Exper. Path.*, 10:226, 1929.
3 Green, M. A.: "Aerosol Penicillin in Allergic Patients," *Annals of Int. Med.*, 31:260, 1944.
4 Schatz, A., Bugie, E. and Waksman, S. A.: "Streptomycin, a Substance Exhibiting Antibiotic Activity Against Gram-Positive and Gram-Negative Bacteria," *Proc. Soc. Exper. Biol. and Med.*, 55:66, 1944.
5 Duggar, B. M.: Science News Letter, 54:69, 1948.
6 Ehrlich, J., Gottlieb, D., Burkholder, P. R., Anderson, L. E. and Pridham, T. G.: "Streptomyces Venezuelae, N. Sp., the Source of Chloromycetin," *J. Bact.*, 56:457, 1948.
7 Long, P. H., Schoenbach, E. B., Bliss, E. A., Bryer, M. S. and Chandler, C. A.: "Experimental and Clinical Use of Polymyxin, Chloromycetin and Aureomycin," *California Med.*, 70:157, 1949.
8 Waksman, S. A.: "Origin and Nature of Antibiotics," *Amer. J. of Med.*, 7:85, 1949.
9 Finland, M., Collins, H. S., Gocke, T. M. and Wells, E. B.: "Present Status of Aureomycin Therapy," *Ann. of Int. Med.*, 31:39, 1949.
10 Nichols, D. R. and Herrel, W. E.: "Penicillin in the Treatment of Actinomycosis," *J. Lab. and Clin. Med.*, 33:521, 1948.
11 Schafer, W. L.: "Streptothricosis: Report of a Case of Recovery," *U. S. Naval Bull.*, 48:399, 1948.
12 Appelbaum, E. and Leff, W. A.: "Occurrence of Superinfections During Antibiotic Therapy," *J.A.M.A.*, 138:119, 1948.
13 Tillet, W. S. and Sherry, S.: "Effect in Patients of Streptococcic Fibrinolysin (Streptokinase) and Streptococcic Desoxyribonuclease on Fibrinous, Purulent and Sanguineous Pleural Exudations," *J. Clin. Investigation*, 28:173, 1949.

Trends in the Use of Antibiotics in Thoracic Surgery

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The discovery of penicillin by Fleming initiated studies that have so sharply accelerated the pace of thoracic surgical advance that many articles appearing on the use of antibiotics are obsolete in whole or in part by the time of publication. It must be recognized at the outset that further masses of data must be painstakingly accumulated before clear-cut indications and dosages can be determined. The excellent cooperative studies being carried out in the Veterans Administration and by others under the direction of the Central Streptomycin Committee have presented extremely valuable data on streptomycin, for example, that have been collected in a surprisingly short time. The tremendous accumulated literature on penicillin has gradually clarified over a longer period a number of problems that have beset the surgeon. Certainly there can be no doubt that with the antibiotics the indications for surgery are being constantly broadened, the complications markedly reduced, and the over-all results immeasurably improved.

It seems superfluous to emphasize that antibiotics, on the other hand, cannot be substituted for good surgical technique and sound surgical judgment. The surgeon must recognize the antibiotics as valuable but necessarily limited adjuncts, and must forego the temptation to lean too heavily on them as a crutch. Unfortunately the indiscriminate use of these agents has become far too common. Russell Brock feels that in England, as many observers note here, undue reliance is being placed on antibiotics to cover poor surgery, and to unjustifiably delay needed operative intervention. The long recognized surgical principles of careful selection of cases, of adequate drainage of suppuration, and of thorough debridement remain unchanged, although the clinical and pathological picture is frequently so altered by the antibiotics that the physician can be easily lulled into a false sense of security.

A large number of chemotherapeutic compounds of biologic origin have been introduced since Fleming's work in 1929. Dubos' tyrothricin has a definite but rather limited topical utility. The more recently discovered aureomycin and chloromycetin would seem to have an increasing application in chest disease, as for

example in Friedlander's infections. Within the past year at least six additional antibiotics of some promise have been introduced, although the efficacy of these remains to be ascertained. One of these, neomycin, may eventually challenge streptomycin in tuberculosis; another, bacitracin, has stimulated encouraging reports regarding its use topically. As yet streptomycin, reported by Waksman and his co-workers in 1944, has been the only antibiotic to approach penicillin in its usefulness to the thoracic surgeon.

Streptomycin

Streptomycin, though effective against a number of organisms, is of particular interest to the chest surgeon because of the bacteriostatic effect it exerts on the tubercle bacillus, as the studies of Hinshaw, Feldman, and others have well demonstrated. A more favorable effect is exerted on fresh exudative and hematogenous tuberculous lesions than on those essentially productive or fibrotic in nature.

Two important considerations, toxicity and the development of streptomycin resistance, have posed serious problems. The first, toxicity, apparently relates to the streptomycin blood level, while the second relates to duration of treatment. Toxic manifestations have been significantly reduced since dosages of one gram per day have been demonstrated to be as effective as the larger dosage schedules previously in use in surgical regimens. Apparently a single dose is quite as satisfactory as divided doses, and is probably less toxic. Dihydrostreptomycin, now being extensively investigated, would appear to be as efficacious as streptomycin and to give rise to fewer toxic reactions. Inasmuch as there has been some doubt thrown on this last contention, there is still question as to whether it will replace streptomycin. We have been using one gram of dihydrostreptomycin in two daily doses almost exclusively during the past 15 months, and have encountered no toxic manifestations of serious nature.

As to resistance, Dubos has sober-mindedly predicted that streptomycin may well have outlived its usefulness within 10 years. The problem can at least partially be met by limiting the period of administration to six weeks or less, and by withholding the drug except in specific indications. Inasmuch as the patient all too often reaches the surgeon after his organisms are already streptomycin fast, Beattie and Blades recommend that streptomycin be reserved for use during the operative period in any case which may be potentially surgical.

The crux of the problem of indications for streptomycin comes down to the question of when will the patient receive the maximum benefit from the drug, assuming that an adequate course

may well produce permanent resistance. The phthisiologist, whether he be internist or surgeon, must ask himself the question, "What is the over-all plan for this patient?" Both Carr and Benjamin Brock are in agreement that the antibiotic should be withheld until this plan can be formulated.

In preparing patients for collapse therapy, undoubtedly a certain number having fresh exudative disease can, with the aid of streptomycin, be brought to the procedure more safely and rapidly. There is honest question, however, whether this is good judgment. Perhaps reliance on the patient's resistance with the aid of recognized conservative management is the wiser course. We would subscribe to the view that if the patient can be brought to collapse therapy without streptomycin, this should, with few exceptions, be the rule. However should the progress of his disease be such that definitive collapse therapy would otherwise be impossible, he should justifiably receive the drug. How frequently streptomycin is warranted in an attempt to avoid collapse therapy altogether is of course beyond the scope of this discussion.

Obviously it is advisable to determine streptomycin resistance prior to a course of streptomycin if the drug has been previously administered. Experimental work now going on would indicate that the administration of para-aminosalicylic acid with streptomycin tends to delay the emergence of resistance, as well as to enhance the inhibitory effect over that obtained with either drug alone. If however resistance has already been demonstrated by culture studies, the administration of PAS alone will probably afford at least some measure of protection. (Domagk's TB-1 may also be of real usefulness in this regard).

Although the intramuscular route is admittedly the best mode of administration, three methods of topical application deserve comment. Our own experience in the treatment of endobronchial tuberculosis by aerosol streptomycin was disappointing as were those of other investigators. The work of Samson, Meissner, and others demonstrating that tuberculous endobronchitis is a deep-seated rather than a superficial disease from a pathological standpoint, undoubtedly explains the equivocal results.

Intrapleural use of streptomycin fell into disrepute when first used in tuberculous empyema. In an early report in 1946 Hinshaw, Feldman, and Pfuetze stated that in seven cases of tuberculous empyema in which streptomycin had been injected only one favorable result was obtained. Encouraged by the mention of one of these seven cases in which a bronchopleural fistula had closed, the senior author successfully expanded a case of tuberculous empyema with bronchopleural fistula which had been refractory to repeated aspirations over a period of five months. One gram

of streptomycin was injected intrapleurally daily, after thorough irrigation with normal saline. The bronchopleural fistula was closed within two weeks, and prompt re-expansion of the lung followed. Three conditions would have to be present to duplicate such a result: (a) a small bronchopleural fistula, (b) the absence of secondary organisms in the empyema, and (c) the absence of a thick fibrin cortex over the lung. In most cases decortication would be preferable.

Various thoracic surgeons have advocated the use of streptomycin intrapleurally following resection and have felt that it provides appreciable protection, particularly when there has been gross contamination of the pleural space. The efficacy of such a procedure is difficult to evaluate in view of the attendant use of streptomycin intramuscularly; the rationale of the procedure, however, is sound. A third topical use of streptomycin in tuberculous sinuses probably needs further investigation. Intramuscular use certainly seems more logical than topical application, in view of the fact that the latter probably cannot reach the more deeply involved tissues.

In the light of our present knowledge of streptomycin in tuberculosis, certain operative usages deserve consideration:

Extrapleural Thoracoplasty: It must be admitted from the figures accumulated by the Veterans Administration and others, that the use of streptomycin prophylactically in thoracoplasty undoubtedly reduces the postoperative morbidity, the incidence of spread and reactivation, and the occurrence of wound infection. On the other hand the technique of thoracoplasty has been so well standardized in the hands of competent thoracic surgeons that complications at the present time are comparatively rare. In the figures from most thoracic clinics spreads or reactivations occurred in from 3 to 6 per cent of cases. This relatively low figure is due, no doubt, to a number of factors: the careful selection of cases, improved surgical and anesthetic techniques, and better postoperative care. In our own series the incidence of significant spreads or reactivations has been below the 3 per cent figure during the past five years. We feel that operating on the thoracoplasty patient in the afternoon, after he has had an opportunity to raise his sputum adequately in the morning, is an important factor in the low incidence of this complication. We have used closed anesthesia, rather than intratracheal as advocated by Murphy and Walkup, who feel that the maintenance of a good bronchial toilet is essential. From the Veterans Administration collected figures, Murphy has reported a reduction in occurrence of spreads from 5.6 to 2.0 per cent by virtue of streptomycin protection in a consecutive series of 1347 thoracoplasty stages. Roughly

half of the group received streptomycin, while the other half served as controls. Wound infections in this same group were reduced from 2.4 to 1.1 per cent. These figures would seem to be statistically significant, although the factors heretofore mentioned have in the hands of some surgeons kept the complications to a comparable figure prior to the advent of streptomycin.

If apparently adequate thoracoplasty fails, as it will in 20 to 35 per cent of cases, the only two procedures feasible for this group with residual cavitation are lobectomy and cavernostomy. Inasmuch as present figures would indicate that streptomycin protection is practically mandatory in resections for tuberculosis, and in the closure of cavernostomy sinuses, it would appear poor judgment to use streptomycin routinely in thoracoplasty in an attempt to benefit less than 6 per cent while jeapardizing the chances of the 20 to 35 per cent who well may need streptomycin protection later and yet be unable to avail themselves of the drug because of resistance. Since it has not been demonstrated that the percentage of cavity closure is higher with streptomycin than without, it is more logical to avoid routine administration of the drug in thoracoplasty, and to use it instead to treat the complications of spread or wound infections in those few cases where they do appear, and to protect the occasional substandard risk. Patients in the older age group, to illustrate, might be justifiable risks for thoracoplasty with the aid of streptomycin, but would not be feasible candidates for resection in any event. It should be mentioned that the Veterans Administration protocols have abandoned the use of streptomycin routinely in thoracoplasty.

If the surgeon has decided that streptomycin should be given, as in cases of severe endobronchial tuberculosis, for example, it is important that the operation be so timed that the patient can be carried through all stages of the procedure before streptomycin resistance would in all likelihood develop.

Of course if a Schede thoracoplasty is performed, and actual tuberculous tissue incised, streptomycin is no doubt indicated. Samson feels that if the thoracoplasty is being done over a mixed empyema streptomycin should be given throughout. He also recommends administration with anterior thoracoplasty stages prior to insertion of a Monaldi catheter in patients with tension cavities, citing that Alexander and Welles both have reported a disproportionate number of spreads in this group. In our own experience with eight cases where the time interval between the preliminary anterior stage and the insertion of the catheter was reduced to a week or less, no spreads occurred but tuberculous wound infection deyeloped several months later in two cases, or 25 per cent, in spite of adequate preoperative and postoperative streptomycin.

We feel the interval between the two procedures was too brief, and have since lengthened it.

Other Collapse Therapy: While results in most types of collapse therapy are better with streptomycin than without it, the considerations pointed out above would constitute serious deterents to the use of streptomycin. Specifically we feel that in closed pneumonolysis no streptomycin should be given unless complications develop. Open pneumonolysis, on the other hand, might need streptomycin coverage for at least a short period because of the more extensive operative measures demanded. Extrapleural pneumothorax might occasionally warrant streptomycin on an individualized basis. As to pneumothorax, it has not been our experience that tension cavities failing to close with pneumothorax could, in many instances, be converted to cavities with adequate bronchial communication by the use of streptomycin alone.

Cavernostomy: In the usual Eloesser flap cavernostomy done in two stages we do not feel it is necessary to administer streptomycin at either stage. However when closure becomes necessary streptomycin is of unquestioned value. Murphy has pointed this out, and under streptomycin protection has closed over 20 cavernostomies, securing primary healing in over 90 per cent. Although our own experience has not been so satisfactory, we heartily subscribe to using streptomycin in such instances. The dosage used has been 1 gram a day for a week prior to operation, and for two or more weeks postoperatively. Because of the secondary infection invariably present, intramuscular penicillin G potassium in doses of 50,000 units or more every three hours is administered.

Pulmonary Decortication: In this procedure, which is still considered of controversial value by some, we feel that protection of the patient by streptomycin is highly desirable, and is mandatory if decortication is being done following tuberculous empyema, or while tuberculous infection of the pleura is present. If a mixed infection is present large doses of penicillin G potassium up to 300,000 units every three hours may also be advisable, in addition to the usual 1 gram of streptomycin as outlined in cavernostomy closure routines. There have been no wound infections and no spreads in our series of seven decortications for tuberculosis. Six of these are considered to have a good functional result with satisfactory obliteration of the space. The other has a small residual pleural pocket at the cupola. We have followed the policy of continuing streptomycin postoperatively until the temperature has been normal for five days. This in all cases has been less than the period of two weeks suggested in most protocols. We think the use of penicillin intramuscularly both preoperatively and post-

operatively is desirable as a protective measure. Usually one of the repository preparations suffices.

Tuberculous Sinuses: The response of tuberculous sinuses to streptomycin therapy has been spectacular, inasmuch as this type of lesion notoriously persisted for many months or years before the advent of streptomycin. Brock reported a series of 60 sinuses in 12 patients with excellent results, and believes that healing can be obtained in 95 per cent of sinus cases treated with streptomycin where free surgical drainage exists. Relapses, as reported by some observers, are usually due to the failure to carry out adequate debridement on all sinuses and infected wounds before beginning streptomycin. If all tuberculous tissue can be excised, and relatively clean tissue approximated, the results are, as Brock has stated, amazingly satisfactory. As in cavernostomy, the addition of penicillin to the chemotherapeutic regimen is highly desirable.

Pulmonary Resection: The evidence strongly supports the conclusion of Murphy and of Moore that streptomycin be considered mandatory before and after every pulmonary resection for tuberculosis where the organisms are not streptomycin fast. Prior to its use as an adjunct in tuberculous resections, 600 cases were reported in the American literature. In this series the total operative mortality was 25 per cent, empyema 12 per cent, and bronchopleural fistula 8 per cent. Overholt reported 104 cases of pulmonary resection without the use of streptomycin between March 31, 1944 and April 5, 1946, with 15 per cent mortality. Bailey had a 25 per cent mortality in 100 pulmonary resections without the use of streptomycin, and noted 18 per cent spreads, 8 per cent bronchopleural fistulas, and 11 per cent empyemas. In 100 comparable cases Bailey used streptomycin and reported an operative mortality of 14 per cent with only 1 per cent tuberculous spreads, 1 per cent bronchopleural fistulas, and 2 per cent empyemas. Figures from the Veterans Administration showed a drop in operative mortality to 4.5 per cent following the use of streptomycin in contrast to the pre-streptomycin rate of 25 per cent.

At the Veterans Hospital at Oteen, North Carolina, 69 pneumonectomies and 64 lobectomies have been done with streptomycin protection. In the pneumonectomy group the operative mortality has been 6.1 per cent, the non-operative 4.5 per cent, the incidence of spreads 6.1 per cent, of bronchopleural fistulas 13 per cent, and of empyemas 3 per cent. In the lobectomy group the operative mortality has been 5.4 per cent, the non-operative 1.7 per cent, spreads 3.6 per cent, fistulas 9 per cent, and empyemas 3 per cent.

When these figures are contrasted with the pre-streptomycin

group of 600 cases reported in the literature, there can be little doubt that streptomycin is a significant factor in the improvement.

At the present time the Oteen group is running a controlled series of resections, giving alternate cases 1 gram of streptomycin one week preoperatively and two weeks postoperatively, the regimen that most thoracic surgeons are recommending. The remainder of the patients serve as controls and receive no streptomycin. The obvious purpose of the study is to answer the question whether such factors as improved operative techniques and better selection of cases might be the ones responsible for the reduction in complications, rather than the streptomycin. The results of this important investigation will not be apparent for at least another year.

Bogen feels that it is wiser for surgeons to withhold streptomycin during and for a short time following resection until evidence of spread or wound infection has actually been observed, whereupon adequate treatment with streptomycin for at least a month or six weeks might better be expected to care for the complication.

Our feeling is that with the present data at hand streptomycin is the responsible factor for the improved statistics. There are undoubtedly other factors, such as the Overholt face down position and improved bronchial closure, that have contributed to the reduction in mortality rate and incidence of complications. We cannot, however, reconcile the denying of streptomycin to patients undergoing as serious a procedure as resection.

There has been some question in our minds as to whether a shorter period than one week of streptomycin preoperatively would not be fully as effective, at least in those cases where the exudative component is of little significance. By the same token we must admit that the postoperative administration for two weeks is also an arbitrary figure, and may, if anything, be too brief to give adequate protection. Careful evaluation of latent spreads in a large group of patients will be necessary before the full value of the drug is apparent. Without question it will always be necessary for the surgeon to exercise individual judgment in considering each new candidate for resection. Because of the non-tuberculous bronchitis undoubtedly present to at least some extent in every case of tuberculosis where the disease is sufficiently far advanced as to demand resection, we have used both nebulized and intramuscular penicillin to prepare patients for operation. As to the continuance of penicillin following resection, we have used the same criterion as in non-tuberculous resections, continuing the penicillin for a period of several days after the return of the temperature to normal. This of course can be done with more

assurance because the surgeon is dealing with infections not having the complex chronicity of tuberculosis.

Pericardectomy: Certainly in those cases where the tubercle bacillus is suspected as the causative agent for the constrictive pericarditis, streptomycin is highly desirable. If the tuberculous infection has adequately subsided and stabilized, the same regimen of streptomycin for a week preoperatively and two weeks postoperatively should be adequate. It well may prove feasible to operate on constrictive pericarditis in a much earlier phase now that streptomycin is available. In such instances it would seem more logical to administer streptomycin for a period of at least three weeks before operation, and to continue it for another three weeks after operation. As in other surgical procedures, the surgeon should always plan his operations for a time when there is at least reasonable assurance that streptomycin resistance cannot yet have developed.

Penicillin

The fact that penicillin is effective against a large number of organisms, principally the gram-positive group, implies that studies should be made to determine penicillin sensitivity before the drug is administered on an empiric basis. The same rule of course applies to all antibiotics. Our impression is that penicillin is being given far too frequently. Fortunately the organisms to be combated are as a whole more short-lived than the tubercle bacillus, and the development of resistance of less importance.

At low levels penicillin is bacteriostatic; at higher levels it is bacteriocidal. For susceptible bacteria there is a minimum concentration that retards growth, a somewhat higher concentration that kills the organisms faster than they multiply, and a still higher concentration that kills them at a maximum rate. Thus the present tendency toward larger doses is a valid one. The ideal therapeutic blood level implies a concentration of penicillin that will kill the most bacteria in the shortest possible time. Since penicillin G potassium will give the highest blood levels, it is probably the most valuable preparation for the surgeon, at least in combating the common postoperative complications susceptible to the drug. We feel that even though the blood level may be raised above the maximal effective level by larger dose schedules, the excess penicillin is not wasted inasmuch as it tends to keep the blood level within the therapeutic range for a longer time and insures a higher tissue level in areas having a poor blood supply.

The so-called repository penicillin preparations, designed to provide prolonged effective blood levels, have proved satisfactory

in our experience for preoperative prophylaxis in those cases in which infection is relatively minimal. In such instances a single daily dose of 400,000 units of the repository preparation is given for a period of one or two days preoperatively. In many patients where the chances of postoperative pneumonia and other infectious complications are small, the same dosage may be continued postoperatively until the temperature is normal for several days.

If on the other hand massive active infection with penicillin-sensitive organisms is present, we use dosages as high as 300,000 units of penicillin G potassium at three hour intervals. Recent work at Bellevue Hospital suggests that even higher doses are sometimes indicated.

We have been particularly interested in aerosol penicillin in the treatment of chronic chest disease, having used it in over 500 cases, and have felt it is of real help in preparing patients for surgery. Admittedly low and ineffective blood levels are obtained with aerosol penicillin. However the purpose of this type of therapy is not to obtain high blood levels, but to obtain high levels on the bronchial mucosal surface. A number of investigators have demonstrated that the bronchial tree can be at least temporarily sterilized after a few days of aerosol therapy. Since this therapy can be timed to carry the patient over the crucial period of surgery itself, particularly in those cases where the bronchus is opened as in resection, the aerosol route should provide considerable protection. We feel rather strongly that bronchoscopy prior to the use of the aerosol antibiotics greatly increases the effectiveness of the inhalation therapy. Siltzbach advocates intratracheal instillation, and claims a 50 per cent drop in sputum volume within 24 hours. He contends the method is of great value in preparing bronchiectatic patients for lobectomy.

Intrapleural administration of penicillin in our practice is largely limited to instillation following routine pneumonectomy and irrigation following contaminated resection. It might be added that careful follow-up is necessary in the latter type of case lest the surgeon be led to consider the contaminated field as having been sterilized rather than rendered temporarily bacteriologically static.

We do not as a rule treat empyema by intrapleural instillation unless the infection is a very early one. Once the pus has thickened, it is far more satisfactory to perform a simple open thoracotomy than to subject the patient to a long series of repeated thoracenteses, with extended expensive hospitalization. There are however exceptional instances in which the use of intrapleural penicillin in empyema may be of great value. We have had the experience of sterilizing three pneumothorax spaces contaminated with penicillin-susceptible organisms without having to reexpand

the pneumothorax to obliterate the space. We have had an equally good result in the case of a right pneumonectomy for lung abscess. Although two courses of penicillin instillation were necessary, this patient escaped without drainage of his empyema space, and continues well to date some five years following his resection. These are admittedly isolated usages.

The problem of penicillin usage can probably best be clarified by considering several disease categories in which it is of value:

Bronchiectasis: In those patients who are being prepared for surgery, bronchoscopy is the first step of the regimen. This is followed by an intensive course of expectorants and postural drainage and antibiotic therapy. The secretions obtained at bronchoscopy can, through smear and culture, provide an accurate picture of the bacterial flora involved. Penicillin, at the rate of 25,000 units, is administered by the aerosol route every three hours during the day for 16 inhalations or more. We add six drops of prothricin to each dose for the shrinking effect and for the action of the tyrothricin on the usually complex endobronchial flora. We have felt that bacitracin combined with a vasoconstrictor may prove superior to prothricin. If streptomycin-sensitive organisms have been found, streptomycin is added to the inhalations. This is doubly important since some of these streptomycin-sensitive organisms may elaborate a penicillinase inhibiting the action of the penicillin.

With the above measures the sputum volume can usually be significantly reduced, and the general condition of the patient considerably improved. Inasmuch as resection for bronchiectasis is almost always an elective procedure, the operation should be postponed until the patient is optimally prepared.

We also order repository penicillin for two or more days preoperatively, or use regular penicillin if considerable infection is present. Postoperatively regular penicillin is administered every three hours. We have rarely seen infection develop in an atelectatic area prior to relief of the block when these measures are carried out.

As previously mentioned penicillin is instilled into the pleural space after removal of the lung, and is sometimes used for irrigation via the intercostal drainage tube in cases of lobectomy and segmental resection. At the time the intercostal tube is removed, 100,000 to 200,000 units of penicillin is injected into the pleural space. In our experience the incidence of empyema has been exceedingly small, as has that of bronchopleural fistula.

Kay, Meade, and Hughes have reported an outstanding series of 220 lobectomies, largely for bronchiectasis, with but one death. All were protected with penicillin both pre and postoperatively. White et al, in a series of 41 patients undergoing lobectomy and

pneumonectomy found no empyemas in the group receiving penicillin, while the pre-penicillin group had 60 per cent empyemas. In the suppurative category all of the control group receiving no penicillin developed empyemas. These investigators point out that penicillin serves to control acute and chronic infection in the pulmonary tissues, and reduces the possibility of postoperative infection. In addition it affords a maximum therapeutic effect at the time the pleura is exposed to bronchial contamination.

Lung Abscess: The adequacy of chemotherapeutic and antibiotic therapy depends to an appreciable extent of course on the duration of the abscess as well as on the causative organisms. As in bronchiectasis, we feel that bronchoscopy should be done immediately to promote adequate bronchial drainage. The same smear and culture studies are made. Penicillin G potassium up to 300,000 units every three hours is administered intramuscularly, and aureomycin 500 mg. is given every three hours by mouth. If gram-negative organisms are recovered from the bronchial secretions, streptomycin is of course added. Bronchoscopy is repeated as often as is needed to maintain good bronchial drainage: this is felt to be exceedingly important, ofttimes helping to transform an anaerobic lesion into a more easily treated aerobic one. Expectorants and postural drainage are continued. If the patient does not improve promptly following these measures open drainage or resection, usually the latter, is indicated.

It can be emphatically stated that antibiotic therapy is not the solution of the lung abscess problem. In our experience with over 200 lung abscesses, almost as high a percentage came to surgery with antibiotics as without. It is of course admitted that this group has been in far better condition for surgery than the pre-antimicrobical series. There has also been a decided drop in the incidence of lung abscess, undoubtedly due to the fact that antibiotic agents have aborted many potential abscesses. It should be stressed that lung abscess patients should be adequately protected at resection with combined antibiotic therapy, since the incidence of empyema and fistula is appreciably greater in this group than in the bronchiectatic one.

Intrathoracic Tumors: All patients undergoing exploratory thoracotomy for intrathoracic tumors can be given repository penicillin for one or two days preoperatively to advantage. Usually aerosol penicillin is given as well. In those cases where no suppurative disease is present, such a regimen will afford adequate prophylaxis against possible bronchial contamination. The repository penicillin is continued postoperatively, but regular penicillin substituted if the expected postoperative morbidity is exceeded. Streptomycin is not given unless bacteriological studies reveal streptomycin-

sensitive organisms. As a whole, intrathoracic explorations have been so free of complications in the hands of most thoracic surgeons when adequate antibiotics have been used, that no physician need have qualms about recommending exploration in doubtful lesions.

When postoperative pneumonia is encountered, large doses of penicillin are given intramuscularly without delay. If prompt clearing does not occur, bronchoscopy is performed. With intratracheal anesthesia, antibiotic protection, and bronchoscopy, chest complications can be reduced to a minimum.

Thoracic Trauma: In cases of early traumatic hemothorax the patient is placed upon large doses of penicillin G potassium intramuscularly at three hour intervals until thoracenteses bring about obliteration of the pleural space by expansion of the lung. In non-infected organized hemothorax the same regimen is usually continued for the short interval until decortication can be undertaken. At the time of operation additional penicillin is instilled into the pleural space. Regular intramuscular penicillin is continued until satisfactory re-expansion and obliteration have occurred, after which time repository penicillin may be substituted if the temperature is not yet within normal ranges. Where decortication is being done for infected hemothorax or for non-tuberculous empyema, large doses of penicillin G potassium for a few days preoperatively and until the space is completely obliterated postoperatively are of exceeding importance. Prompt re-expansion of the lung with healing by primary intention is usually the rule when vigorous suction has been instituted.

The principles of debridement and primary closure, elucidated during the last war, apply of course to management of chest wall wounds, the main deviation from older techniques being the greater leeway granted the surgeon in primary closure of contaminated wounds and in secondary closure of infected wounds under antibiotic protection.

Surgical Diseases of the Esophagus: Before resection is undertaken, the elimination of esophagitis proximal to obstructive lesions will result in less friable tissues for anastomosis, a less dangerous bacterial flora at the operative site, and fewer anastomotic failures. This problem may be managed by attention to oral hygene, daily irrigation of the esophagus with 100 cc. of 5 per cent sodium sulfadiazine, and adequate doses of parenteral penicillin.

At the conclusion of transthoracic operations wherein the esophagus has been opened we routinely introduce 200,000 units of penicillin and 1 gram of streptomycin in 20 cc. of normal saline in the pleural cavity before closure. If the peritoneal cavity has been invaded a similar solution is placed in the abdomen before

closure of the diaphragm. In the postoperative period the patient receives large intramuscular doses of penicillin G potassium, at least 100,000 units every three hours, and is given streptomycin as well. This program, together with improved operative techniques, has eliminated pleural and mediastinal infections except in the occasional patient who develops a gross leak at the anastomosis. Even these patients may sometimes be salvaged by more vigorous antibiotic therapy and judiciously selected and properly timed drainage procedures followed by secondary repair. These principles also apply in treatment of spontaneous, operative, and foreign body perforations of the esophagus.

Surgical Diseases of the Heart and Great Vessels: Most surgeons have used prophylactic schedules of the antibiotics to cover resections and anastomoses of great vessels and surgery of the heart valves and septa. This therapy has apparently been directed at prevention of bacterial implantation on newly created raw surfaces. In this field it may be debatable whether antibiotic protection should be purchased at the price of the reported increased tendency toward intravascular clotting produced by the antibiotics.

After drainage of suppurative pericarditis, topical application of the proper agent, as indicated by bacteriologic studies, is obtained by introducing the agent in solution by catheter under low gravity pressure around and posterior to the heart after daily gentle separation of new adhesions with the gloved finger. Using 1,000,000 units of penicillin in 250 cc. of normal saline at body temperature the benefits of lavage and irrigation are attained simultaneously with specific drug therapy. This procedure, as well as intramuscular administration of the agent, is continued daily until space obliteration is obtained.

Inasmuch as many authorities, as has been mentioned by Troutman and Vincent, now predict a recovery rate of 90 per cent or better in cases of streptococcus viridans subacute bacterial endocarditis uncomplicated by patent ductus arteriosus, with the aid of adequate doses of penicillin (up to 20,000,000 units per day), the routine use of the drug in cases complicated by patent ductus is obviously indicated. This in spite of the observation of Touroff and Vesell that the blood stream infection has been cured in certain cases in which the vegetations were limited to the heart valves simply by interruption of the patent duct alone. Taussig has pointed out that if in such cases sterilization of the blood stream is not immediate, the infection may be overcome with the aid of penicillin.

In cases in which the vegetations also involve the vessel wall, as well as the heart valves, the results of interruption of the patent ductus are poor with regard to sterilization of the blood stream.

Furthermore the operation is rendered more hazardous because of the increased friability of the vessel wall. In such cases vigorous penicillin therapy is indicated without question.

The utilization of streptomycin in cases of penicillin-resistant strains of streptococcus fecalis is of course warranted, as reported by Guss and others. The addition of heparin is advised in order to prevent local thrombophlebitis.

SUMMARY

Antibiotics have revolutionized thoracic surgery. As yet streptomycin and penicillin far outweigh the other antibiotics in their value to the thoracic surgeon.

Because resistance to streptomycin develops rapidly and is permanent, this antibiotic should not be used indiscriminately, but should be restricted to specific indications. The use of streptomycin as an adjunct in tuberculosis surgery has extended operative indications, and has made possible safer and more effective pulmonary resection, decortication, cavernostomy, closure of tuberculous sinuses, and pericardectomy. The administration of 1 gram a day, in one or two doses, is recommended for periods of six weeks or less.

In the light of present knowledge the use of streptomycin would not seem justified in routine thoracoplasty, inasmuch as complications are already minimal. Its use is rarely justified in other forms of collapse therapy.

Penicillin has proved of particular value in the surgery of bronchiectasis and lung abscess, in thoracic trauma, in exploration for intrathoracic tumors, in esophageal surgery, and in surgery of the heart and great vessels.

The present trend is toward larger doses of penicillin, with penicillin G potassium the preparation of choice in active infection. In surgery, repository and aerosol penicillin are primarily applicable in prophylaxis.

REFERENCES

1 Brock, Russell: Personal Communication.
2 Dubos, Rene: Personal Communication.
3 Beattie, E. J. and Blades, Brian: "Use of Streptomycin in Surgical Patients," *J.A.M.A.*, 139:902, 1949
4 Carr, Duane: Personal Communication.
5 Brock, Benjamin: Personal Communication.
6 Samson, P. C.: "Mucosal Tuberculosis of Bronchi and Trachea," *Dis. of Chest*, 4:15, 1938.
7 Meissner, W. A.: "Surgical Pathology of Endobronchial Tuberculosis," *Dis. of Chest*, 11:18, 1945.
8 Hinshaw, H. C., Feldman, W. H. and Pfuetze, K. H.: "Treatment of Tuberculosis with Streptomycin," *J.A.M.A.*, 132:778, 1946.
9 Walkup, H. E.: Personal Communication.
10 Murphy, J. D.: "Streptomycin in the Surgery of Pulmonary Tuberculosis," *S.G.O.*, 87:546, 1948.

11 Samson, P. C.: "The Prophylactic Administration of Streptomycin Before and After Major Thoracic Surgical Operations," *Am. Rev. Tuberc.*, 58:38, 1948.
12 Murphy, J. D.: "Cavernostomy for Residual Cavity After Thoracoplasty. Early Closure of Cavernostomy Openings under Streptomycin Protection," *Minutes of the 6th Streptomycin Conference,* Oct. 21-24, 1948, p. 149.
13 Brock, B. L.: "Streptomycin in the Treatment of Tuberculous Sinuses," *Am. Rev. Tuberc.*, 58:35, 1948.
14 Moore, J. A., Murphy, J. D. and Elrod, P. D.: "The Use of Streptomycin in Pulmonary Tuberculosis," *Surg. Clinics of N. Am.*, 28:1543, 1948, and Personal Communication.
15 Overholt, R. H., Langer, L., Szypulski, J. T. and Wilson, N. J.: "Pulmonary Resection in the Treatment of Tuberculosis: Present Day Technique and Results," *J. Thoracic Surg.*, 15:384, 1946.
16 Bogen, Emil: Discussion of Paper by Beattie and Blades, *J.A.M.A.*, 139:906, 1949.
17 Waterman, D. H. and Domm, S. E.: "The Treatment of Chronic Bronchitis and Allied Bronchial Affections with Bronchoscopy and Aerosol Antibiotics," In press.
18 Siltzbach, L. E.: "Intratracheal Penicillin Therapy in Suppurative Bronchiectasis," *Arch. Int. Med.*, 79:570, 1947.
19 Kay, E. B., Meade, R. H. Jr. and Hughes, F. A.: "Surgical Treatment of Bronchiectasis," *Annals of Int. Med.*, 26:1, 1947.
20 White, W. L., Burnett, W. E., Bailey, C. P., Rosemond, G. P., Norris, C. W., Favorite, G. O., Spaulding, E. H., Bondi, A. Jr. and Fowler, R. H.: "Use of Penicillin in Prevention of Postoperative Empyema Following Lung Resection," *J.A.M.A.*, 126: 1016, 1944.
21 Miller, C. C. and Sweet, R. H.: "The Occurrence of Infection After Pulmonary Resection," *New Eng. J. Med.*, 240:589, 1949.
22 Troutman, W. B. and Vincent, D. J.: "Subacute Bacterial Endocarditis, Satisfactory Treatment of Two Cases with Massive Doses of Penicillin," *South. Med. J.*, 41:334, 1948.
23 Touroff, A. S. W. and Vesell, H.: "Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus: Recovery Following Surgical Treatment," *J.A.M.A.*, 115:1270, 1940.
24 Taussig, H. B.: "Congenital Malformations of the Heart," *The Commonwealth Fund,* New York, 1947.
25 Guss, J. H.: "Successful Treatment of Subacute Bacterial Endocarditis with Streptomycin," *Am. Heart J.*, 35:662, 1948.

Aerosol Therapy of Bronchopulmonary Diseases*

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With the advent of the sulfa drug era in modern medicine the treatment of some bronchopulmonary diseases, especially the more common pneumonias, has become successful. This point can be verified by comparing mortality rates and complications before and after the addition of various sulfa drug preparations to the physician's therapeutic armamentarium. Improvement in the technique and results achieved in the treatment of various bronchopulmonary diseases was further enhanced by the discovery of penicillin and streptomycin until, today, the mortality rate and complications in properly managed cases of the commonly encountered lobar and bronchopneumonias are, by comparison, practically negligible. There remains, however, a large group of acute and chronic common bronchopulmonary diseases which have not responded as favorably as one would expect even with the increased utilization of these newer forms of therapy when they are administered by the usual systemic routes. In particular, the results achieved in the treatment of such conditions as lung abscess, bronchitis and bronchiectasis have been manifestly unsatisfactory as a rule. The very nature of the pathologic processes involved in such conditions explains the usual equivocal or actually unsatisfactory results obtained when the treatment is confined to a systemic attack on the disease. When specific and indicated drugs are administered by the various systemic routes, in these instances, it appears that they are unable to penetrate the pulmonary tissue barriers in sufficient quantity to establish effective therapeutic levels at the site of the infection.[8] Clinicians have long recognized the fact, therefore, that in certain bronchopulmonary diseases a local as well as a systemic attack upon the underlying disease process is an essential prerequisite for the achievement of lasting cures or, at least, palliative results. Consequently, with this thought in mind, various chemotherapeutic agents, especially the sulfa drugs, were administered by nebulization or direct bronchoscopic instillation.[1] By far and large, the results obtained were not encouraging. With the advent of the

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Many of the original illustrations are omitted because of limited space.

various antibiotic agents, however, the aerosol therapy of many usually resistant acute and chronic bronchopulmonary diseases has resulted in truly remarkable and unanticipated successes.[2,3,5-10] Many patients who would have previously been considered as hopeless cases and perhaps relegated to lives of chronic invalidism, and in many instances eventual death, have benefited immeasurably from the increased utilization of antibiotic aerosols administered either singly or in various combinations.

The theory and practice of direct topical administration of therapeutic agents in the treatment of certain bronchopulmonary disorders are in themselves quite ancient.[3] It was only after the advent of antibiotics, however, that the aerosol treatment of certain previously resistant bronchopulmonary diseases could be undertaken with any degree of expected success. Innumerable methods and types of apparatus have been recommended by equally innumerable investigators who unhesitatingly claim superiority for their method of aerosol administration. The literature on the subject of aerosol therapy is not only voluminous but also somewhat confusing. Consequently, many patients have been deprived of the acknowledged benefits of this form of therapy because a large number of general practitioners, internists and other physicians interested in the treatment of bronchopulmonary diseases have considered the procedure too complicated, theoretical or expensive for successful implementation in their own practices. The purpose of this communication is to describe a simple method of administering aerosol therapy, and to record the experiences acquired, problems encountered and results achieved in the treatment of various bronchopulmonary disorders in a large group of patients.

Apparatus: The Vaponefrin nebulizer (glass) was used exclusively in the treatment of these cases. The aerosol is vaporized by means of oxygen at a steady flow of four (4) liters per minute. At a convenient point in the rubber tubing which connects the oxygen regulator valve and the nebulizer, a glass "Y" tube is inserted. The patient is taught to occlude the free opening of the "Y" tube with a convenient finger-tip for a duration of time equal in length to the duration of each inspiratory effort. A tight-fitting cork is inserted in the carburetor opening. In this manner, nebulization occurs only when the free opening of the "Y" tube is occluded and treatment is thus effected with a minimum of waste and effort. The vaporizer spout is introduced to a point slightly beyond the inner border of the lips and the patient inhales the aerosol through the open mouth.

In those instances where it is necessary to treat concomitant sinus infections, a glass reduction tube is attached to the spout

of the nebulizer, and the aerosol is delivered directly into each nostril for alternating periods of time corresponding to the duration of each inspiratory effort. The patient is seated in a comfortable position, and the solution (2 cc.) is usually nebulized in a period of 30 minutes. For home treatment, manual vaporization may be accomplished with little effort and with encouraging results. As a general rule, it is advisable not to exceed a volume of 2.0 cc. or 2.5 cc. of the solution which is to be nebulized at each treatment. Larger amounts are apt to be tiring to the patient. A few sensitive individuals will complain of vertigo when oxygen is used, but this symptom may be disregarded.

In order to avoid mechanical difficulties encountered because of the occlusion of the small capillary jet tubes in the nebulizer, it is thoroughly cleansed and sterilized immediately following each treatment. After washing the residue of the medication out of the carburetor, it is a good practice to direct a flow of oxygen or compressed air through the nebulizer jet for a short period of time in order to insure absolute patency of the capillary tubing It is then placed in bichromate cleaning solution until its next utilization. If this technique is followed and if only medications suitable for aerosol therapy are utilized, one will experience little or no difficulty in the operation of this simple apparatus.

Technique and Drugs: The bacterial flora of the bronchopulmonary secretions of patients who are considered suitable candidates for aerosol therapy should be determined before treatment is instituted. This can be accomplished easily by examining a Gram stain of a satisfactory specimen of sputum microscopically. Although the exact nature of the offending microorganism or organisms may not be ascertained accurately by this method, it, nevertheless, serves to classify the responsible etiologic agent as Gram-negative or Gram-positive bacteria. This information is usually adequate and facilitates the rapid institution of effective therapeutic measures. The effect of the aerosol therapy upon the bronchopulmonary infection can then be followed by repeated Gram stain examinations of the sputum. If the anticipated therapeutic response is not achieved, then further bacteriologic studies should be carried out in order to identify accurately the offending microorganism.

The non-tuberculous pathogens responsible for bronchopulmonary infections are generally Gram-positive and will usually respond to penicillin therapy. In a small percentage of cases, however, after the Gram-positive organism is erradicated, the bacterial flora will undergo a relative and absolute increase in both the variety and number of Gram-negative bacteria. Although these organisms are commonly considered to be non-pathogenic, as

secondary invaders they are unquestionably responsible for a protracted period of disability and therapeutic failures in many instances. From clinical observation only, it appears that they assume frequently some of the pathogenic qualities of their Gram-positive neighbors. Recent published observations of other investigators tend to support this opinion.[2,11] To overcome this difficulty and the previous presence of penicillin resistant bacteria encountered in the aerosol therapy of bronchopulmonary disorders, it is then necessary to supplement the treatment with streptomycin. These two antibiotics used in combination can generally handle all of the more common bronchopulmonary infections. When streptomycin and penicillin are used simultaneously, it is advisable not to use the calcium salt of penicillin with streptomycin sulfate since calcium sulfate is precipitated in this solution and interferes with the mechanical efficiency of the nebulizer. The dosage of penicillin employed varies from 25,000 units to 50,000 units per cc. and the dosage of streptomycin usually varies from 50,000 units (.05 gm.) to 100,000 units (.1 gm.) per cc. Normal saline is used in preference to distilled water as a solvent for either of these antibiotics. Although the physician's individual preference may vary concerning this choice, it is the author's opinion that normal saline is less irritating to mucous membranes than distilled water. Additionally, it is felt that crystalline potassium penicillin is the penicillin of choice in this form of therapy. Some patients will be found, in the course of events, who have been previously sensitized to penicillin or streptomycin, or both. In this event, unless the allergic manifestations are alarming, treatment is continued with the assistance of one of the presently available antihistaminic drugs.

In the absence of any of the acknowledged contraindications, the addition of a vasoconstrictor and decongestant agent to the aerosol solution has been a routine procedure in the treatment of these patients. More recently it has been our practice to use those preparations which have an added amount of thyrothricin* in order to obtain the additional antibacterial effects of this antibiotic. In this manner it is possible to relieve the edema and spasm of the bronchial tree which are commonly associated with bronchopulmonary disorders. The disturbing symptoms which accompany these pathologic changes are noticeably benefited by the addition of a suitable vasoconstrictor and decongestant agent. Furthermore, the presence of tyrothricin, in our experience, usually prevents the rapid multiplication of the Gram-negative bacteria and precludes the use of supplementary streptomycin therapy to

*Sharp & Dohme's Prothricin; and Wyeth's Edryl.

combat this complication.* This precautionary measure not only serves as a valuable prophylactic measure clinically, but also helps to conserve the patient's economy. In some instances where the spasm and edema are marked and do not readily respond to this form of therapy, the utilization of adrenalin 1:100 in the aerosol solution may become necessary. In the treatment of asthmatic individuals and those suffering from emphysema, this is a common practice. One cc. of either prothricin, edryl, vaponefrin or adrenalin 1:100 are usually employed in each treatment. These agents can be used as solvents for penicillin or streptomycin in order to decrease the volume of the aerosol solution. The latter practice is helpful in the treatment of those patients who operate the nebulizer manually. The amount of effort required to nebulize large volumes of aerosol is tiring and occasionally predisposes to an uncooperative patient.

Although this communication is designed primarily to stress the use of penicillin and streptomycin aerosol therapy, one cannot neglect to mention briefly in passing that many other drugs can be prepared in suitable solution for aerosol therapy. For example, certain sulfa drug preparations are quite suitable for this purpose although the results obtained are inconstant. Suitably prepared solutions of aminophyllin may be utilized in attacks of asthma, and the author has used iodide preparations in the treatment of fungus infections. By means of the aerosol apparatus it is also possible to prepare patients for radiopaque studies of the bronchial tree and pulmonary segments. This can usually be accomplished by the nebulization of as little as 2 cc. of a 4 per cent cocaine solution with or without added adrenalin. Complete and dependable anesthesia of the tracheobronchial mucosa is the rule with this method and satisfactory bronchograms are obtained with uniform regularity.

Method of Treatment—General Considerations: The number of daily treatments, length of treatment and the dosage of the antibiotic agent used depend upon the nature and severity of the illness. Initially, the more serious cases are treated four times daily. The number of daily treatments and drug dosage should be adjusted frequently to parallel the clinical progress in each case. Besides antibiotic aerosol therapy, indicated general and symptomatic measures in the treatment of each disorder should not be neglected. Many patients require large doses of expectorant cough mixtures in order to loosen the tenacious bronchial

*Since the preparation of this manuscript we have found the use of Soluthricin, 2.5 per cent (Sharp and Dohme), very effective for this purpose and non-toxic. From 0.06 cc. to 0.1 cc. may be employed per cc. of aerosol solution.

secretions. The author has found Brown's Mixture with added ammonium chloride effective in producing this result. In other cases, syrup of hydriodic acid was utilized successfully. Aside from its expectorant qualities, it has been found equally useful as a palatable prophylactic and therapeutic measure in the treatment of some primary and secondary fungus infections. The type of expectorant medication used is, nevertheless, purely a matter of individual preference and patient reaction. More important is the daily inspection of the quantity and nature of the sputum which determines the efficacy of the preparation used. Expectorants should be administered in the largest tolerated dosage in order to achieve the maximum therapeutic benefit.

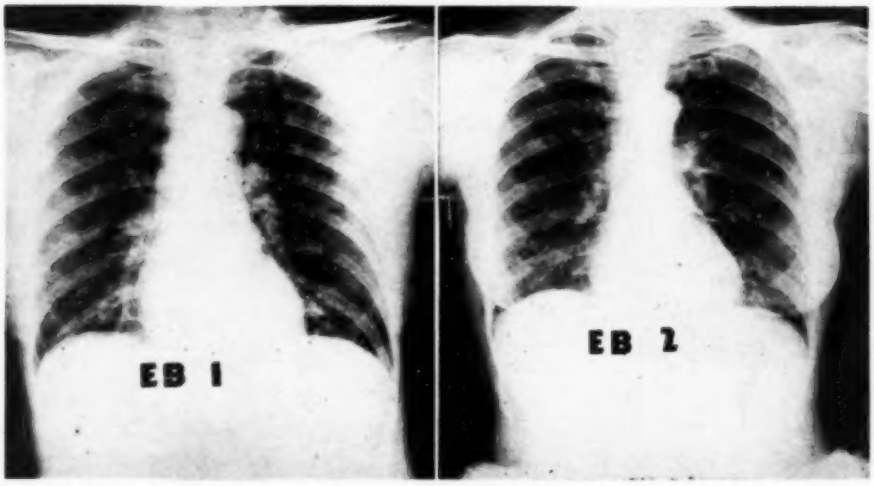
Those individuals suffering from bronchiectasis and lung abscess should be carefully instructed in the technique of correct postural drainage. Of course, in those patients who are chronically ill and debilitated, the state of nutrition must receive careful attention, and the possibility of blood transfusions in these individuals should always be considered. Likewise, a large number of these patients experience difficulty in obtaining the required amount of rest and sleep and, for this reason, adequate amounts of sedative drugs should be used liberally. Agents which are primarily intended to suppress the cough reflex, on the other hand, should be used in the minimal effective dosage and only when absolutely necessary. In many cases the use of aerosol therapy by itself will be sufficient to control or cure the underlying bronchopulmonary disorder. Until we were able to demonstrate the unquestionable efficacy of aerosol therapy in these cases, it was utilized primarily as an adjunct type of treatment, and patients received large doses of various chemotherapeutic and antibiotic agents concomitantly by the systemic route. It was soon found, however, that in numerous instances the simultaneous systemic administration of chemotherapeutic and antibiotic agents was clinically unnecessary and an economic waste. Once the systemic manifestations of the illness are adequately controlled, specific drug therapy can be confined exclusively to the aerosol route of administration.

In addition to following each patient's progress by the usual clinical signs and symptoms, frequent x-ray examinations of the chest and microscopic examinations of properly stained bronchopulmonary secretions should be evaluated at regular intervals. These precautions are necessary in order to manage each case intelligently and effectively. As the physician gains wider experience in the use of aerosol therapy, he will be emphatically impressed with the individual variations in each disease and in each patient. Reliable indices of the clinical progress in cases of bronchiectasis and lung abscess can be maintained by careful obser-

vation of the nature and amount of the daily sputum (Case 5) When the physician is satisfied that the disease has been adequately controlled, patients can be instructed in the manual use of the nebulizer and permitted to follow the prescribed treatment at home. In cases of lung abscess, frequent follow-up x-ray examinations are imperative because of the notorious tendency toward recurrence even months after the infection has been apparently controlled (Case 6). If, in properly selected cases, the expected therapeutic response with aerosol therapy is not achieved in a reasonable length of time, especially in the case of lung abscesses, bronchoscopic examination and aspiration of the bronchial tree are indicated.

Case Histories: The following case histories and roentgenograms are presented in an effort to demonstrate the results achieved and problems encountered in a representative group of patients suffering from common varieties of resistant, acute and chronic, bronchopulmonary disorders treated with aerosol therapy.

Case 1: E.B., a 65-year-old white spinster. For 20 years suffered from severe sinusitis and bronchitis with frequent acute exacerbations. The patient's condition had deteriorated steadily over this long period of years until she was practically a bedridden invalid. Among the innumerable therapeutic measures tried, systemic administration of various sulfa drug preparations, penicillin and streptomycin in large amounts and for prolonged periods of time either individually or as combined therapy, likewise, failed to arrest the steady progress of the disease. When first seen several million units of both penicillin and streptomycin together with large amounts of sulfadiazine had been administered systemically for several weeks without any appreciable effect upon the course of the illness. The roentgenogram showed evidence of patchy pneumonitis (Fig. EB 1). Clinically, she had an almost continuous exhausting and productive cough, and at times temperature spikes as high



CASE 1

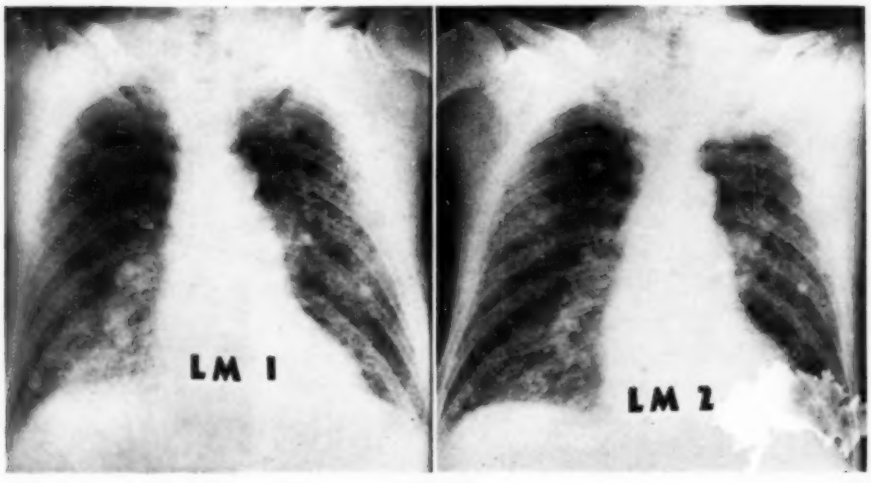
as 103 degrees F. (oral) were recorded. Aerosol penicillin and streptomycin therapy by nasal and oral routes produced a rapid subsidence of all symptoms and signs. Systemic administration of all chemotherapeutic and antibiotic agents was discontinued after 48 hours. A roentgenogram of the chest (Fig. EB 2) 10 days after the institution of aerosol therapy showed remarkable clearing. This improvement has been maintained for the past 14 months. Infrequent minor relapses are rapidly controlled by penicillin aerosol therapy. During this period of time, she has gained much weight and strength and is now able to carry on a practically normal existence.

Comment: The author prefers the descriptive terminology of bronchosinus disease as a label for the frequent combination of sinusitis and bronchitis. From the therapeutic standpoint it is really unimportant to determine whether the sinusitis preceded the bronchitis or vice versa. This controversial problem, in itself, has long been the subject of numerous investigations but is still undecided. The simultaneous treatment of both conditions is the important therapeutic consideration in this illness. Both areas of infection must be controlled in order to obtain satisfactory and lasting results. Lingering infection in either area predisposes to reinfection of the other. Furthermore, in order to avoid serious relapses, aggressive antibiotic aerosol therapy should be instituted at the first sign of recurrence. In this particular case, as well as in many other bronchopulmonary disorders, the rapidity of roentgenographic resolution of the disease process does not necessarily parallel the clinical progress of the disease. Frequently, abnormalities in serial roentgenograms of the chest can be detected long after the patient is completely relieved of all clinical signs and symptoms. In bronchosinus disease the clinical improvement, as a rule, is unusually rapid and easy to sustain. Nevertheless, in order to obtain optimal results from the use of aerosol therapy in bronchosinus disease, treatment should be energetic in the earliest and acute stages of the illness. Many cases of otherwise intractable chronic bronchosinus disease could be avoided in this manner.

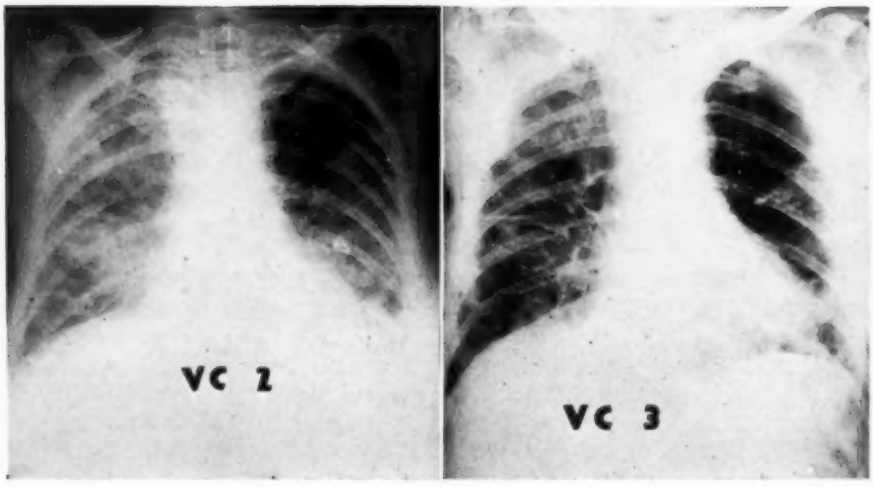
Case 2: L.M. is a 66-year-old white male who worked in a foundry practically all of his employable years. He was retired because of disabling silicosis. During the past 10 years there were numerous episodes of superimposed bronchopneumonia. The therapeutic effectiveness of various sulfa drugs and antibiotic agents became less satisfactory with each recurrence until at the time of the most recent bronchopneumonic complication (Fig. LM 1) response to systemic therapy was practically negligible. Aerosol penicillin therapy together with adrenalin 1:100 produced remarkable alleviation of all clinical signs and symptoms. Within six days there was marked improvement in the roentgenogram (Fig. LM 2). However, his general condition deteriorated rapidly and he died from respiratory failure during the course of his hospitalization. Necropsy substantiated the clinical diagnosis.

Case 3: V.C., a 52-year-old white female. Radical mastectomy had been performed for cancer of the right breast. Additionally, received intensive radiation therapy. Subsequently, developed radiation pneumonitis. The systemic administration of large doses of sulfa drugs, penicillin and streptomycin not only failed to control the illness, but there was actual progression of clinical signs and symptoms (Fig. VC 2). Four days after aerosol penicillin therapy was instituted there was marked clinical and x-ray evidence of improvement (Fig. VC 3). Extensive metastatic lesions demonstrated at autopsy, nevertheless, were responsible for her eventual death.

Comment: In these instances, although treatment failed to save the patient's life, death in each case was the result of the underlying disease process and not the secondary infection. The clinical improvement and the increased comfort to the patient



CASE 2

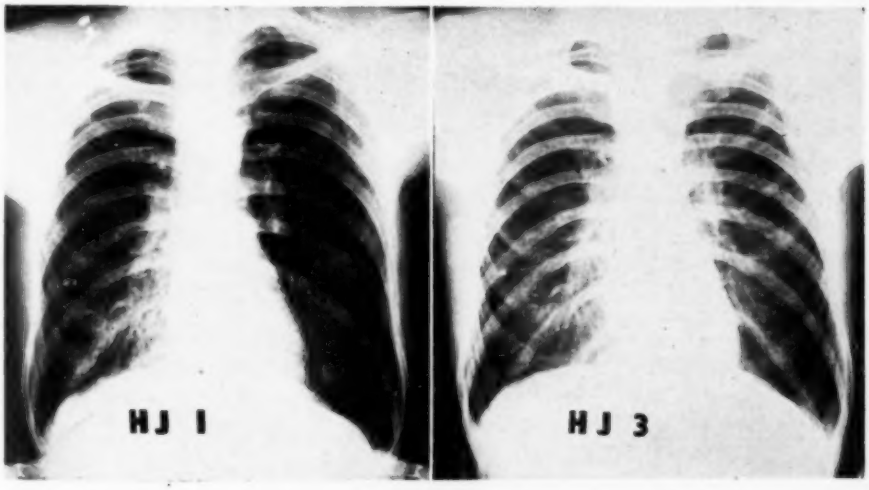


CASE 3

warranted the use of aerosol therapy. Systemic administration of various drugs was useless because the blood supply to the involved area was completely disrupted and rendered inadequate by the primary condition. This type of disease is an excellent indication for aerosol therapy.

Case 4: H.J., a 45-year-old white carpenter was treated for "flu" in November, 1946. Although the patient returned to his usual occupation after several weeks of illness, recovery was never complete. There was a persistent productive and annoying cough with daily small elevations of temperature. A roentgenogram of his chest on March 31, 1947 revealed a dense area of infiltration in the para-cardiac area of the right lower lobe, which extended to the diaphragm (Fig. HJ 1). Bronchograms were not obtained because of the patient's refusal to submit to the procedure. After a careful review of this patient's illness, it was decided that he was suffering from pseudo-bronchiectasis. The original diagnosis of "flu" was changed to primary atypical pneumonia of undetermined etiology. Systemic sulfa drug and penicillin treatment had failed to influence this complication of the original disease and the patient continued to lose weight and strength. Nine days after the institution of aerosol penicillin and streptomycin therapy there was marked clinical and roentgenographic improvement. Three and one-half months later re-ray of the chest showed almost complete resolution of the original infiltration (Fig. HJ 3). Aerosol penicillin and streptomycin therapy in this case was administered for about 10 days, and there has been no recurrence of the disease during the past year.

Comment: The term pseudobronchiectasis was first used by Brian Blades.[4] Although many investigators question the existence of this entity, the author shares his opinion without reservation. Since the publication of Blades' original observation, numerous cases of primary atypical pneumonia of undetermined etiology have been encountered in which the syndrome of pseudo-



CASE 4

bronchiectasis was recognized in the course of a protracted convalescence. The results obtained with aerosol therapy in this case again demonstrate the superiority of this form of treatment in selected cases.

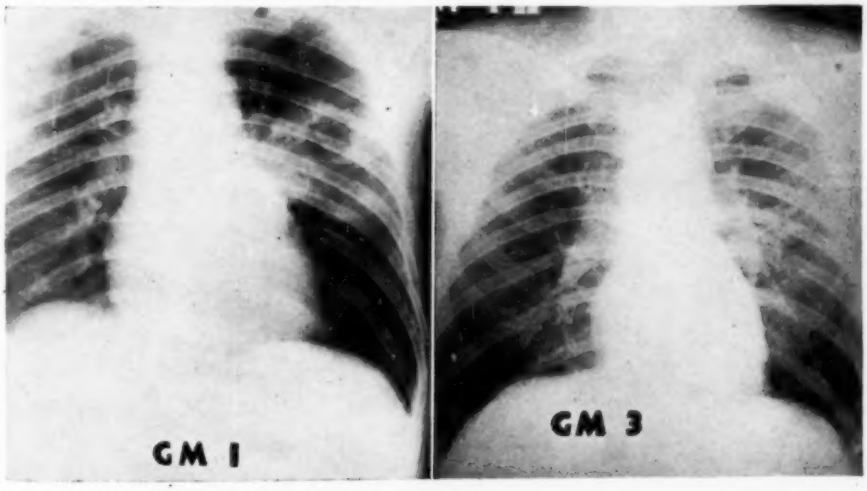
Case 5: L.H., a 37-year-old white male was told that he had bronchiectasis five years previously. Cough and expectoration of foul smelling purulent material continued unabated and increased in spite of many types of treatment. When first seen he was raising between 12 and 16 ounces of sputum daily. A bronchogram revealed the existence of dilated and distorted bronchi in both lower lobes. No attempt was made to outline any other pulmonary segments. Aerosol penicillin and streptomycin therapy, together with postural drainage and other general supportive measures, produced marked improvement in this patient's condition. The quantity of sputum decreased rapidly until, at the end of 12 days of treatment, he was raising only from 15 to 20 cc. of a watery type sputum. Only rare bacterial organisms were demonstrated by direct smear and stain.

Comment: The use of aerosol antibiotic therapy in long-standing cases of bronchiectasis is not intended as a curative measure. It is used primarily as a palliative procedure only to achieve symptomatic improvement. Many patient's lives have been made more pleasant since the advent of this form of therapy. Additionally, aerosol antibiotic therapy is valuable as a preoperative measure in the preparation of these patients for lobectomy or pneumonectomy.[6,9] Aerosol therapy preoperatively is indicated in all patients who are candidates for major pulmonary surgical procedures. The routine preoperative aerosol preparation of these patients will generally minimize the surgical risks and complications. Control of the pulmonary infection will improve the general clinical status and make patients more suitable candidates for surgery. Many patients who, in the past, would have been denied the benefits of surgical therapy because of their debilitated condition can now be converted to suitable candidates for surgery. Satisfactory tracheobronchial anesthesia prior to instillation of lipiodol in this case was obtained after aerosol administration of 2 cc. of a solution of cocaine 4 per cent with a small amount of added adrenalin. Although this patient was apprehensive, a satisfactory bronchogram of the desired pulmonary segments was procured. This method of obtaining effective and complete tracheobronchial anesthesia has been used successfully in many patients, not only preparatory to bronchographic studies but also in preparation for bronchoscopic examinations. The cough reflex is usually effectively abolished, and a satisfactory anesthesia is obtained with a minimum of anesthetic agent and technical effort. Even apprehensive individuals are able to cooperate and

satisfactory bronchograms are the rule because of the total type of anesthesia.

Case 6: G.M., a 50-year-old white male was found to be suffering from a lung abscess six months following the extraction of several teeth (Fig. GM 1, recumbent portable x-ray). Although he was quite ill most of this time, he did not seek medical treatment. Instead he drank about one pint of whiskey daily to control his symptoms. Large systemic doses of sulfa drugs and penicillin failed to produce any clinical improvement. Ten days after the institution of aerosol penicillin therapy together with other general measures indicated in the treatment of pulmonary abscess, roentgenographic, as well as clinical improvement was marked. Two months later there was no roentgenographic evidence of the original pulmonary abscess (Fig. GM 3). However, a chronic mild cough productive of small amounts of sputum persisted. This patient was never very cooperative and soon after discharge from the hospital abandoned all recommended treatment. Nevertheless, his progress remained satisfactory until one year later. At that time two thin-walled cavities reappeared at the site of the original lesion. He again refused medical attention and has not been heard from since.

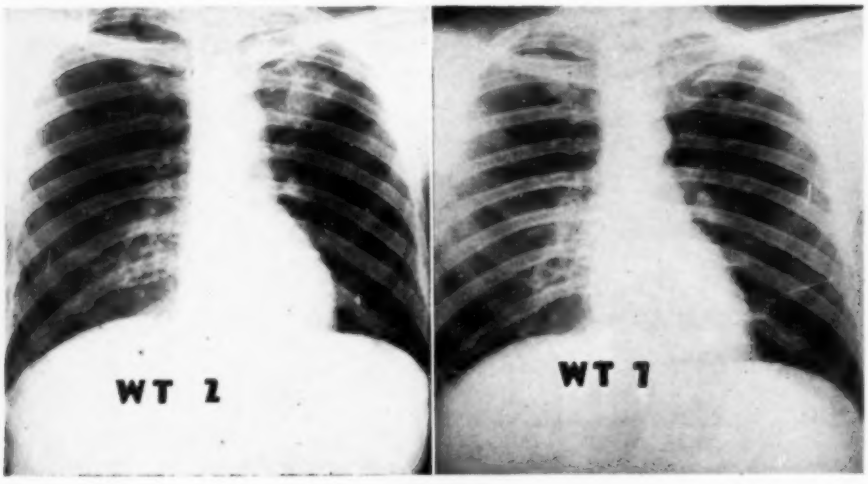
Comment: Ordinarily one would not expect a pulmonary abscess of this long-standing to respond to conservative medical management. Actually, in this particular case, aerosol penicillin therapy was instituted with the express purpose of preparing this patient for lobectomy. The unexpected clinical and roentgenographic improvement, however, precluded the necessity for surgical intervention. Recurrence of the original abscess in this case demonstrated the importance of repeated frequent serial roentgenographic chest examination of all patients in whom apparent cures are obtained. Although therapeutic results are more consistent and satisfactory in the acute lung abscesses, occasional permanent



CASE 6

successes in the chronic variety warrant a therapeutic trial with aerosol therapy in all cases. Even if aerosol therapy fails to cure the abscess, the usual general improvement in the patient's condition and at least partial sterilization of the bronchopulmonary tissue will minimize the surgical risk.

Case 7: W.T., a 37-year-old white male had all of his teeth extracted on the advice of his physician as a therapeutic measure for a low backache. Although penicillin was administered systemically in adequate prophylactic doses at the time of dental surgery, a few days later he developed chills and fever. There was roentgenographic evidence of dense infiltration in the left upper and right lower lobes. Systemic sulfadiazine and penicillin were administered in large doses without appreciable effect upon the clinical or roentgenographic course of the disease. There was some clearing of the infiltration in the right lower lobe, but the lesion in the left upper lobe excavated (Fig. WT 1). At this point aerosol penicillin therapy together with systemic sulfa drug administration, postural drainage and general supportive measures were instituted. After five days there was additional clearing of the lesion in the right lower lobe with noticeable dimunition of the lesion in the left upper lobe. During the next five days the patient's progress clinically and roentgenographically was unchanged. The original predominantly Gram-positive flora of the sputum had disappeared completely, and there was an absolute increase in the number of Gram-negative organisms. At this point streptomycin was added to the aerosol solution. Seven days later there was remarkable improvement clinically and roentgenographically. None of the original Gram-negative or Gram-positive bacteria could be detected. During this time, however, there was a luxuriant growth of Monilia albicans on several occasions. Repeated diligent efforts to demonstrate acid-fast organisms by various methods failed. Aerosol iodide therapy was substituted for the antibiotic therapy. Although much decreased in number, the monilia persisted in the sputum. Systemic iodide administration and intravenous aqueous gentian violet was used as a last resort. Although the clinical signs and symptoms abated under this



CASE 7

rather heroic therapy and the roentgenogram showed marked improvement, occasional monilia could still be demonstrated on direct smear. Twelve months later there was no clinical or laboratory evidence of relapse. Instead, the roentgenogram shows sustained improvement (Fig. WT 7). This patient has been engaged in his previous occupation for the past eight months and has regained his former weight and strength.

Comment: The commentary on case six above is applicable to this case in its entirety. However, additionally important therapeutic observations and practices are demonstrated in this case which seemed to resist all therapeutic efforts. The development of pathogenic qualities by supposedly non-pathogenic secondary invaders was responsible for the protracted resistant illness in this case. The imperative necessity for daily examinations of the bacterial flora of the sputum, by whatever indicated bacteriologic procedure, is thus adequately demonstrated. Without this knowledge adequate and indicated therapy is difficult and invites therapeutic failures. The beneficial results of aerosol therapy in this type of case can be anticipated only if the therapeutic management is altered to parallel the constantly changing clinical and bacteriological picture.

Furthermore, in view of the fact that a lung abscess developed in this case despite the prophylactic administration of adequate amounts of penicillin systemically, reconsideration of the acceptable principles of prophylaxis is warranted. Three possible explanations for the pathogenesis of the ultimate disease should be considered in this case. In the first place, since systemic penicillin administration failed as a prophylactic measure, one is justified in questioning the efficacy and wisdom of this practice at least as regards lung abscesses. Perhaps aerosol prophylaxis is the procedure of choice in these instances. In the second place, should one consider the possibility that penicillin resistant microorganisms were either present or developed following the prophylactic use of this agent. Finally, was the pulmonary anatomy in this particular case previously altered by some antecedent disease process so as to preclude the anticipated effectiveness of prophylactic systemic penicillin administration. These possibilities although based on the presumptive observations of one case, nevertheless, are worthy of serious consideration and investigation. Until a satisfactory answer is forthcoming, aerosol antibiotic prophylaxis with, or without, systemic antibiotic administration is certainly worthy of empirical trial.

Conclusion: In addition to the cases reported above, the author has observed the beneficial effects of aerosol therapy in a large number and variety of other common acute and chronic bronchopulmonary disorders. Palliative effects of this form of therapy

were uniformly striking in bronchial asthma and emphysema. Similar improvement was noticed in one case of polycystic lung disease and in one case of Ayerza's disease. In several cases of infectious asthma aerosol antibiotic therapy produced lasting remissions as well as palliative results. Aerosol antibiotic therapy is extremely valuable as a palliative and prophylactic measure in the preparation of patients for pulmonary surgery and bronchoscopy. Not infrequently, the preoperative aerosol preparation of patients for major pulmonary surgery results in unanticipated permanent cures. The use of aerosol therapy prophylactically and therapeutically is indicated in all bronchopulmonary disorders which do not respond to the systemic administration of antibiotics and other agents.

Some investigators have reported adequate and even more effective therapeutic antibiotic blood levels following aerosol administration.[3,10] This method of antibiotic administration is, nevertheless, not recommended as a form of systemic therapy since absorption from the pulmonary tissue is influenced by too many unpredictable and variable factors.[3,10] Therefore, it is felt that aerosol therapy should be reserved exclusively for those cases in which systemic antibiotic administration fails or is not expected to achieve the desired therapeutic results.

SUMMARY

1) A simple method for the administration of antibiotic and other indicated aerosol therapy in the treatment of acute and chronic bronchopulmonary disorders has been presented.

2) The results achieved and problems encountered in a representative group of patients suffering from common varieties of ordinarily resistant, acute and chronic, bronchopulmonary disorders treated with aerosol therapy have been recorded.

3) The importance of palliative, prophylactic and therapeutic aerosol administration in the medical and surgical management of bronchopulmonary diseases has been adequately demonstrated.

RESUMEN

1) Se presenta un método sencillo para la administración de antibióticos y otros medicamentos indicados por la via del aerosol.

2) Se refieren los resultados obtenidos y los problemas que se encuentran en un grupo representativo de las diferentes variedades de enfermedades broncopulmonares ordinariamente resistentes, usando el aerosol.

3) La importancia del aerosol usado como paliativo, preventivo y terapéutico en el dominio de los padecimientos de órden médico o quirúrgico, ha sido demostrado adecuadamente.

REFERENCES

1 Applebaum, I. L.: "The Treatment of Bronchial Lesions by the Inhalation of Nebulized Solutions of Sodium Sulfathiazole," *Dis of Chest,* 10:415, 1944.
2 Barach, A. L., Garthwaite, B. and Rule, C.: "The Use of Penicillin Aerosol in Bronchopulmonary and Sinus Infections," *N. Y. State J. of Med.,* 46:1703, 1946.
3 Barach, A. L., Silberstein, F. H., Oppenheimer, E. T., Hunter, T. and Soroka, M.: "Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Lung Abscess; Preliminary Report," *Annals of Int. Med.,* 22:485, 1945.
4 Blades, B. and Dugan, D. J.: "Pseudobronchiectasis," *Jour. of Thor. Surg.,* 13:40, 1944.
5 Bryson, V., Sansome, E. and Laskin, S.: "Aerosolization of Penicillin Solutions," *Science,* 100:33, 1944.
6 Edlin, J. S.: "Discussion of Inhalation Therapy," *Dis. of Chest,* 13:308, 1947.
7 Hanks, R. J.: "Nebulized Penicillin in the Treatment of Respiratory Infections," *Dis. of Chest,* 12:242, 1946.
8 Levine, E. R.: "Inhalation Therapy in Chronic Bronchial Infections," *Dis. of Chest,* 13:295, 1947.
9 Olsen, A. M.: "Discussion of Inhalation Therapy," *Dis. of Chest,* 13: 310, 1947.
10 Segal, M. and Ryer, C. M.: "Penicillin Aerosolization in Treatment of Serious Respiratory Infections: A Preliminary Report," *New England J. of Med.,* 233:747, 1945.
11 Weinstein, L.: "The Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin and Penicillin," *Am. J. Med. Sc.,* 214:56, 1947.

Discussion

DAVID WATERMAN, M.D., F.C.C.P.
Knoxville, Tennessee

The administration of aerosol antibiotics and other drugs can be a simple thing and we have found that the use of the same apparatus Dr. Friedman has mentioned has been most satisfactory, and that more complicated methods are unnecessary.

Any chest man has patients referred to him who have had chronic cough for years, have been treated by all the usual expectorants, and gallons of cough syrup, intramuscular penicillin, sometimes inadequate aerosol penicillin and have had no relief. We became interested, particularly in the chronic bronchitis group, three of four years ago and purely experimentally, started what we felt was a fairly well controlled clinical study as to what could be done.

For bronchiectatics we have been using bronchoscopy and penicillin by aerosol or intramuscularly in preparation for surgery and in palliation for a long time. We have studied about 340 patients with chronic bronchitis.

We treated a group with bronchoscopy alone, with definite benefit. From a group treated with aerosol alone and also a group with

bronchoscopy and aerosol. Recently we have been studying a group with bronchoscopy and penicillin dust but are not as well satisfied with that as we are with aerosol.

There is advantages in bronchoscoping a good number of this group as mechanical aid following bronchoscopy. After cleaning out the bronchial tree, aerosol treatment is started.

The second advantage of bronchoscopy is in diagnosis. We have picked up five carcinomas of the lung on bronchoscopy either on direct or indirect signs or through the study of the secretions later for tumor cells that were previously unsuspected. We also see the reaction of the bronchial tree and from which branches the secretion is coming.

Aerosol is not a substitute for surgical therapy. We occasionally get brilliant results from aerosol and it deserves its place but the majority of them will have to be treated as we have treated them in the past. We have the clinical impression that this regime has benefited the bronchitis group much more than anything we have ever done.

Our regime is as follows: After the patient has bronchoscopy, he is started on aerosol penicillin five times a day, 25,000 units every three hours. At the same time we give expectorants and postural drainage routine even though the patient may not have a great deal of sputum. We get five different studies on the sputum, first a smear for spirochetes and other organisms; second, a culture for identification of organisms; third, a tuberculosis concentration culture; fourth, a fungus culture, and fifth, we make an autogenous vaccine which seems to work better when made from bronchial secretions than from expectorated sputum and is certainly more efficacious than stock vaccines. This group of patients have permanent pulmonary damage and we are not going to give them a new set of lungs; all we are doing is controlling the infectious factor, but if we can do that, many of them are able to live relatively normal lives. We invariably take these patients off smoking and I dont believe there is any single part of the treatment that is more important as far as prolonging the benefit is concerned.

A. WORTH HOBBY, M.D., F.C.C.P.
Atlanta, Georgia

We have been using aerosol with air and the results are as good as with oxygen.

Some believe the concentration of the solutions of antispasmodics is rather high. Dr. Friedman is correct in his use of that

concentration. Antispasmodics in aerosol are only about 50 per cent absorbed.

I have been using Iodolac as an inhalation for some time but it is a little too weak. Aeorsol itself has proved beneficial but I believe we may shorten treatment by using aerosol and intramuscular administration at the same time. I want to commend search for acid-fast bacilli in every coughing patient before the administration of any kind of treatment. It is surprising in how many of them we find acid-fast bacilli with an entirely negative x-ray film. Whether the acid-fast bacilli are tubercle bacilli or not is our problem.

M. JAY FLIPSE, M.D., F.C.C.P.
Miami, Florida

Aerosol may be of benefit in long continued asthma that has had no relief from other measures of therapy. In some instances, this type of therapy will give spectacular response, particularly if the aerosol is combined with ¼ cc. of 1 per cent aqueous synephrin. As a rule, we do not find it necessary to use large doses, 25,000 units per cc. in normal saline given three or four times a day, either alone or in combination with intramuscular penicillin.

Closing Remarks

Louis L. Friedman, M.D., F.C.C.P., Birmingham, Alabama: From my original remarks and those of the various discussants, it is apparent that we are only beginning to understand and realize the multiple applications of aerosol therapy. Opinion regarding the correct therapeutic application of aerosol antibiotic therapy is divided. I do not share Dr. Hobby's feeling regarding the use of simultaneous parenteral therapy except in a few instances. As a rule, those cases which are suitable for aerosol therapy have already had a trial with systemic therapy. One of the chief indications for aerosol antibiotic therapy is the failure of treatment by the oral or parenteral routes. Additionally, in the treatment of bronchiectasis, it is well to stress the fact that aerosol therapy is no substitute for surgical treatment. It should be considered as a palliative procedure, and a preparatory measure for surgery only. Likewise, in lung abscesses which do not respond to a fair trial with aerosol therapy, the internist should not resitate to recommend surgical intervention.

When aerosol therapy is used in treatment of bronchopulmonary

disorders, it is important to study the bacterial flora of the secretions regularly and to make the necessary adjustments in the antibiotic therapy as indicated. The number of agents which can be used as aerosols is practically limitless and depends only upon their ability to enter into a satisfactory solution for nebulization.

I have recently used aerosol antihistaminic therapy in the treatment of bronchial asthma. Benadryl, injectable, as dispensed by Parke, Davis and Company is a satisfactory drug for this purpose. Ten milligrams (1 cc.) of this solution is the usual dose. However, the amount used in each patient and in each treatment depends upon the individual response. When the indication exists, one may administer combined aerosol antihistaminic — sympathomimetic mixtures. A more detailed report of the work with aerosol Benadryl will appear in an early issue of the *Southern Medical Journal*. The drug acts as a bronchodialator and expectorant agent. We have used it in combination with antibiotics in the treatment of bronchopulmonary infections with noticeable benefit. In more than 200 cases observed and studied to date we have not observed any local or systemic allergic response to penicillin or any other antibiotic when benadryl has been included in the aerosol solution.

Treatment of Tuberculosis with Promizole: A Clinical Investigation with Matched Controls

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H. C. HINSHAW, M.D.,[3] J. A. MYERS, M.D., F.C.C.P.[4]
and K. H. PFUETZE, M.D., F.C.C.P.[5]
Minneapolis, Minnesota

Beginning in 1940, it appeared likely that derivatives of diaminodiphenylsulfones, such as promin offered new hope for the development of specific antibacterial agents against this most common of chronic infectious diseases of the human race. Very quickly chemists instituted a program to develop synthetic drugs of increasing efficacy and decreasing toxicity. The compound named "4, 2'-diaminophenyl-5'-thiazolesulfone" (promizole) was subjected to extensive experimental studies at the Institute of Experimental Medicine, Mayo Foundation and was shown to be a moderately effective drug of low toxicity for animals. Preliminary clinical studies at the Mayo Clinic and Mineral Springs Sanatorium demonstrated that it was a drug of low toxicity to human beings but that its therapeutic efficacy was not demonstrable to a degree adequate to permit recommending the drug. Therefore a controlled clinical study appeared necessary.

In carrying out this study our group had three objectives:

(1) To explore the possibilities of evolving a technic of clinical study to evaluate therapeutic agents in a protean disease such as tuberculosis. (2) To determine if promizole exerts a recognizable antibacterial effect in certain clearly definable types of pulmonary tuberculosis. (3) To make available to the inmates of mental hospitals of Minnesota any therapeutic benefits possible. These unfortunate persons have access to little or no direct therapeutic measures such as collapse treatment and surgery and are often unable to cooperate with bed rest treatment.

This project was instituted in the autumn of 1943. At that time, there was a population of approximately 14,000 inmates in the hospitals for the mentally ill of Minnesota. Of this group there were over 2,000 who showed some evidence of reinfection type tuberculosis by x-ray. More than 1350 films extending through

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[2]Mayo Foundation, Rochester, Minnesota.
[3]Formerly, Mayo Clinic, Rochester, Minnesota. Now, Stanford University Medical School.
[4]University of Minnesota Medical School.
[5]Mineral Springs Sanatorium, Cannon Falls, Minnesota.

The Promizole used in this study was furnished through the courtesy of Parke, Davis and Company, Detroit, Michigan.

several years of observation were available on patients in nine mental hospitals with facilities to cooperate in the study.

Patients were selected for inclusion in this study on the basis of x-ray findings primarily. All patients whose disease had tended to improve spontaneously were excluded and those patients whose disease was of chronic nature were excluded. We felt it necessary to prove by serial films that the disease process was unstable and progressive and that there was a substantial component of exudative bronchopneumonic tuberculosis of apparently reversible type before a patient could be included in this investigation. After a patient had been selected for this study it was then necessary to pair him with another patient of about the same age whose disease was of similar quality, extent and distribution and to secure unanimous agreement of the investigators that the outlook of each one of the pair was apparently the same. Needless to say, many highly interesting and otherwise suitable cases were excluded because it was not possible to find a comparable patient to pair with the candidate for treatment. When a pair of patients had thus been matched to the approval of the group, a coin was tossed to determine which of the two patients would receive treatment with promizole and which would be given a placebo treatment consisting of Brewer's yeast tablets.

Adequate clinical records were maintained and films on each patient taken at monthly intervals. A number of patients selected for treatment were excluded due to their inability to cooperate because of their psychiatric condition. Oral medication was often refused. Others were excluded because of toxic reactions which did not permit treatment in adequate dosage for sufficiently long periods of time.

Evaluation of Results:

Results were evaluated on the basis of roentgenographic improvement alone. Films were reviewed without the observer having knowledge as to whether the patients belonged in the treated or in the control group. Because of the type of disease in the cases selected the progression was usually so obvious and death so frequently occurred during the period of study that no particular difficulty was encountered in evaluation.

Results Obtained:

The following table shows the status of the project when it was concluded in December 1944. It will be noted that only 24 pairs (48 patients) finally qualified for inclusion in this table. Reference to the last column will show that two-thirds of all patients were either dead or worse by that time and that only 15 per cent

had shown improvement, which was usually of only slight degree. It will also be noted that there is little detectable difference between patients in the treated series and those in the control series.

Treatment of Pulmonary Tuberculosis with Promizole (December 1944)

	Controls	Patients Treated	Total Patients	Per cent
Died early (within 30 days)	5	3	8	
Died later	4	4	8	66
Worse	8	8	16	
No change	6	3	9	19
Slight improvement	1	4	5	
Moderate improvement	0	1	1	15
Marked improvement	0	1	1	
TOTAL PATIENTS	24	24	48	

SUMMARY

Evidence developed by his study indicated that the severe progressive, potentially fatal type of bronchopneumonic tuberculosis selected for treatment with promizole did not respond to such medication given under the conditions of this experiment.

It is quite possible that the handicaps imposed were too severe to be overcome. It is also possible that patients with associated mental disease are less likely to respond favorably to therapy than individuals with normal mentality.

Subsequent experience with streptomycin has demonstrated to the satisfaction of this group of investigators that a large percentage of the patients selected for this study would have made at least temporary improvement with streptomycin therapy had this drug been available at that time.

Tuberculosis and Antihistaminics*

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I. General and Pharmacologic Considerations:

Synthetic antihistaminic substances, first discovered in 1933 by Fourneau and Bovet[1] while seeking a means of combatting the physiologic effects of histamine, have now been used in a large number of fields. The indications have been extended beyond the point of sound pharmacologic judgement and to this day reports are being published which are nothing short of fantastic.

Their mode of action, from the antianaphylactic standpoint, is based on the histamine theory of sensitivity (Lewis[2]) related in large measure to anaphylaxis, allergy, and to histamine poisoning. There is little doubt that histamine is an important factor in anaphylaxis in animals as in human allergy. In an individual in contact with an antigen to which he has been sensitized, a reaction occurs between antigen and its specific antibody which, liberating histamine or a substance analogous to histamine, provokes anaphylactic shock. Histamine is furthermore a chemical substance present under normal conditions in tissue and it has been shown by Katz[3] that all allergic reactions provoke its liberation. In addition the various antihistaminic products react in such a fashion in anaphylactic conditions as to leave little doubt of the role played by histamine in accidents of this type. The still imperfect techniques which are used to measure blood histamine today in patients with allergic conditions do not allow confirmation, although the similarity of results in certain clinical conditions as well as in laboratories are certainly in favor of this hypothesis.

The activity of these antihistaminic substances is demonstrated in certain cases accompanying conditions of capillary permeability of which urticaria, angioneurotic edema, vasomotor rhinitis are examples while in other clinical conditions such as asthma or dermatitis, their indications remain restricted to cases where the allergic origin of the phenomena can be proved readily. In still other clinical states particularly in the area of the nervous system they do not act by virtue of their antihistaminic property but

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rather by those pharmacologic attributes which are apparent in other synthetic substances.

There are three general types of antihistaminic agents which have been recognized and listed by Bovet.[4]

1) Those products with selective properties related to histamine itself through the mediation of histaminergic substances of the pyridine group:

a) derived from aminopyridine: neo-antergan, pyribenzamine, histadyl, chlorothene,

b) derived from pyrimidine: neo-hetramine.

2) Those products which because they are analagous in structure and pharmacologic action are related to sympathetic poisons, and are either sympathicolytic or sympathicomimetic:

a) Phenol ethers: 929 F.,

b) derived from the aniline group: 1571 F., antergan, diatrine,

c) derived from the imidazoline group: antistine,

d) derived from the tetrahydropyridendene group: theophorine.

3) Those products which are antagonistic to acetylcholine with antihistaminic action and severe spasmolytic properties:

a) Benzyl ethers and its derivatives: benadryl, decaprine, histaphene, antadril,

b) derived from the phenotiazine group: phenergan (RP3277), amydril, pyrrozolate,

c) diphenylaminopropane and derivatives: aspasan, trimetone.

All of these products have varying degrees of toxicity and in many instances are poorly tolerated in humans. The antianaphylactic power of these compounds as well as their action on the Schultz-Dale phenomenon does not parallel their antihistaminic action. Furthermore they all present certain pharmacologic properties which although varying in considerable degree may be summarized as follows:

a) They prevent the spasm of the smooth muscle of the uterus, intestine, and bronchi produced by histamine, through a reaction comparable to atropine but to a considerably less degree.

b) They prevent contraction and relaxation of blood vessels and by this means prevent increased capillary permeability.

c) They have a local anaesthetic action. This prevention of cutaneous reaction to histamine whether provoked by irritants or allergens can not be attributed to an antihistaminic effect if this local anaesthetic action can not be eliminated by other appropriate means (Loew[5]).

It is readily seen that these substances do not have a strict specificity, but this point is not really appreciated. On the other hand there is as yet no unanimity of opinion regarding the mechanism of antianaphylactic action.

II. *Tuberculous Allergy:*

In view of the efficiency of these different compounds in certain allergic conditions, it was but a short step to attempt their use in tuberculosis. It should be noted that the word allergy, introduced in 1908 by von Pirquet and used in the sense of "altered reaction" produced and continues to produce considerable confusion. Tuberculous allergy may be differentiated from the phenomenon of anaphylaxis on several different points as demonstrated in laboratory experiments. It is actually possible to provoke anaphylaxis to pure tuberculoprotein by injecting it into a laboratory animal free of tuberculous infection. On the other hand it is absolutely impossible to provoke an anaphylactic reaction in any animal already infected with tuberculosis and the reaction will be totally different.

In the normal animal sensitized to tuberculoprotein, an anaphylactic reaction will occur characterized by:

An immediate acute response within 15 minutes,
No cutaneous reaction, no Arthus phenomenon (Corper[6]),
The reaction may be passively transferred,
The reaction may be transferred to lineal descendants.

This reaction then is a humoral response due to circulating antibodies in blood and body fluids producing an immediate response.

In the animal infected previously with tuberculosis there will be an allergy characterized by:

No acute intoxication, requiring hours to produce a fatal reaction and appearing only after one, six or 24 hours,
A definite positive cutaneous reaction,
The allergic state is not passively transferred,
The allergic state is not an inherited characteristic.

In the latter situation this is more of a tissue response, the antibodies present being fixed to the cell structure producing a delayed reaction. There are obviously two dissimilar reactions in tuberculosis. While the anaphylactic type of sensitization can be established through the injection of pure tuberculoprotein in a virgin organism, this same substance is a chemically extracted toxic material and does not produce the same reaction as the tubercle bacillus in vivo. The special allergic type of sensitization can be established only in an organism previously exposed to a bacillary infection and must be considered as a type of bacillary sensitization.

Certain investigators seem to consider these reactions as similar and believe that there is a common principle basic in these phenomena. It is felt that the different forms of sensitivity are effects resulting from the interreaction of antigen and antibody under

different physiopathologic conditions but probably liberating a homologous toxic substance. It is possible but not proved and up to this time not demonstrated that in the tuberculin reaction there is actually a liberation of histamine. If antihistaminic agents can have any effect in clinical tuberculosis it must be therefore by some other mechanism.

From what has already been presented it seems impossible at this time to say that there is a type of tissue or cell other than involuntary muscle or vascular endothelium which can be directly sensitized to an antigen-antibody reaction. This must be similar in all respects to those produced by direct action of histamine or a similar substance on the same organs in an anaphylactic reaction (Dale and Laidlow,[7] and Rich[8]). In tuberculosis, a type of bacillary sensitivity can exist in the total absence of all anaphylactic sensitivity to tuberculin. That is why one may say that in bacillary sensitization, involuntary muscle as well as vascular endothelium are not sensitized, a fact well proved in vitro and in vivo and that the antibody is bound up intimately in the individual cells. Therefore any tissue which does not have a good capillary bed can be sensitized to the action of the specific antigen in the bacillary type of sensitization but will not respond to the action of antihistaminics. On the other hand anaphylactic phenomena are produced only in tissues where a larger blood supply is present and will respond to the administration of antihistaminic substances. This may explain why in bacillary sensitization the circulating antigen in the blood can induce an inflammatory process, necrosis, or hemorrhage in any area of the organism which is involved and the focus of infection will show a "focal reaction," a rare occurrence in anaphylaxis described, however, by Arthus and explained by him as due to the use of an impure material.

Many authors feel that under certain circumstances in clinical tuberculosis a typical anaphylactic reaction to tuberculin may occur during infection, superimposed on the bacillary type of sensitization. Corper[9] as well as others believe that this concept is only of academic interest in tuberculous animals as well as humans and is of so little importance as not to be worthy of too lengthy discussion.

Such a situation actually may be observed under the following circumstances:

1) In massive dissemination.

2) In pulmonary cortical types adjacent to pleura, a tissue extremely sensitive itself and with a large absorbable surface.

A considerable depression in cutaneous sensitivity may be produced, probably due to some effect on the vascular or inflamma-

tory response of the organism rather than to autotuberculinization or tuberculin autointoxication, for the liberation of tuberculin in the body has never been proved. This latter point is of considerable clinical importance and has not been too well recognized. These types of depressed reaction especially following massive dissemination are generally of short duration, followed as a rule by a temporary increase in tuberculin sensitivity, probably due to the mobilization of large numbers of tubercle bacilli. By virtue of their action on vascular tissue, antihistaminics may have some value in this area during the acute stage (vascular blockade?). However, recent experiences of Halpern and Reber on the influence of antihistaminics on the evolution of experimental microbial infection tend to prove that such employment of antihistaminics, in paralyzing the organization of local inflammatory defenses, favor microbial dissemination. This would tend to contraindicate the use of antihistaminics in local or focal infections. Actual experimental data in animals, infected with Salmonella typhimurium and treated with phenergan (RP3277), showed a mortality through septicemia three times higher than that in control animals.

Can one say then that in chronic forms of tuberculosis any type of desensitization is possible through the use of antihistaminics or by any other method? Desensitization as a form of treatment has been tried and continues to be utilized by a few clinicians. Utilizing Besredka's technique of injecting patients with progressively increasing doses of tuberculin, it has been possible to give as much as 10 cc. of undiluted tuberculin (Bauer[10]), an amount many hundreds or thousands of times that which the patient would have reacted to before sensitization. Is this however a true desensitization? It is rather an extreme tolerance because if desensitization with tuberculin produces an inhibition or alteration of sensitizing antibodies, this does not free the body of its bacilli which will resensitize the tissue as soon as treatment is discontinued and sometimes will provoke a much greater sensitivity in the immediate future. Actual tissue necrosis may occur at the site of tuberculin injection. The obvious importance of focal reactions, considered as a valuable feature in treatment in the past, need not be discussed here. If antihistaminics possess a similar desensitizing effect, should they not similarly be feared, rather than utilized?

III. *The Use of Antihistaminics in Tuberculosis:*

Although numerous investigators have utilized the antihistaminic compounds: Rolland[11] with antergan, Vallery-Radot, Hamburger and Halpern[12] with phenergan, no real benefit from treat-

ment has been reported in France to date. In 1943 Boquet and Breton[13] in their experimental trials were unable to demonstrate in guinea pigs a negative tuberculin response after prolonged subcutaneous injections of the earlier antihistaminic agents. Guy,[14] was unable to obtain any effect in five patients by the use of large doses of pyribenzamine by mouth. Criep, Levine and Aaron[15] could not influence the Mantoux reaction in tuberculous animals using pyribenzamine and rutin by oral route, intradermal injection, iontophoresis or the injection of a mixture of tuberculin and pyribenzamine.

The cutaneous reaction to tuberculin is obviously too variable to be considered as a precise test. It is influenced by meteorologic variations, the state of the peripheral vessels, the acquired sensitivity of the skin and many other factors. On the other hand, the antihistaminics having a local anaesthetic action may in themselves upset further the value of the test. For all these reasons the actual test result may be questioned.

The only optimistic report to date which does not accept within its framework the foregoing physiopathologic concepts, is that of Judd and Henderson[16] presented before the American College of Allergists in April 1949. These investigators used benadryl, pyribenzamine, theophorine and neohetramine in the different forms of tuberculosis both pulmonary and extrapulmonary. In the latter group there were cases of lymph node involvement, larynx, and one case complicated by erythema nodosum. Doses were given of 50 mgm. three times daily, increasing gradually up to a maximum of 500 mgm. according to the patient's tolerance. The patients were followed by tuberculin test, x-ray, pulse, weight, appetite and other subjective symptoms. A dramatic improvement was noted in the x-rays in some patients after a short period of treatment, and it was similarly possible to demonstrate the return of the pathological lesion if treatment was stopped with return of improvement as soon as treatment was again instituted. The sputum also was decreased and the cutaneous reaction seemed less positive throughout the period of treatment. The best results were apparently obtained in the exudative lesions while the fibrocaseous responded less well paralleling the action of streptomycin.

In some cases the antihistaminics were used simultaneously with streptomycin and the authors felt sure that the results with the combined drugs were better than if they were used separately. In the discussion Wittich[17] indicated that other workers had found that neohetramine was effective for the protection of animals against experimental tuberculosis in approximately half the cases, although no specific action against the bacillus had been de-

monstrated in vitro. We have no personal knowledge of this quoted work. The hypothesis was projected that through the suppression of tuberculin sensitivity or some other product of the bacillus, the normal defenses would be better capable of combatting the infection.

In view of this enthusiastic report, through the cooperation of Merck and Company, the following combination of antihistaminic drugs were tried on 30 patients with tuberculosis; neo-antergan and the new product phenergan (RP3277) described by Halpern and Ducrot[18] in 1946, whose action is considerably greater than that of all known antihistaminic substances and much more prolonged. This product had already been tried in France in 1947 by Vallery-Radot, Blamoutier and Halpern[19] in tuberculosis without any influence on the allergic manifestations of tuberculosis or on the intradermal reaction to tuberculin.

No attempt was made in this study to choose special cases for treatment and among those included were cases with far advanced lesions while others had lesions of less importance either exudative or fibrocaseous.

The following dosage schedule was used: Three hundred mgm. of neo-antergan were given daily, divided into fractional doses through the day. In addition 25 mgm. of phenergan was given at bed-time because of the sedative and hypnotic effect noted in the use of this product. The patients noted almost immediately that sleep was considerably better since the use of the antihistaminics.

The compounds were well tolerated generally although there were occasional complaints of drowsiness, dizziness, headaches and dryness of the mouth. In two instances it was necessary to discontinue medication because of vomiting, nausea, vertigo, and in one, a severe tremor.

We have chosen to evaluate the treatment in our cases with the following criteria: X-rays, volume of sputum, sedimentation rate, weight, and subjective complaints. We have not used the skin reaction for the reasons of variability noted previously. The following is a summary of the results. It is to be noted that the results are given for only 28 of the 30 cases since in two cases, treatment was discontinued because of intolerance to the drug at an early date so that the treatment could not be evaluated.

	X-ray	Sputum Volume	Sedimentation Rate	Weight
Slightly improved	8	5	12	14
No change	20	18	8	9
Worse	..	5	8	5

During the course of treatment 12 patients received streptomycin just prior to or simultaneously with the antihistaminics in a dose of one gram daily for 28 days. It should be noted that in general the most suggestive radiologic improvement occurred in this group. Another two patients who did not receive streptomycin also showed significant improvement. The first was a case of diffuse acute pleurisy complicating pneumothorax where the sputum had been negative for approximately four months, and in whom the antihistaminics quickly reduced the temperature and fluid formation in less than six days. The second patient had exudative lesions in both upper lobes which showed only slight retrogression following a course of streptomycin in March 1949. When the antihistaminics were begun, the sputum became converted in one month, the most recent x-rays showing an almost complete clearing. It should be noted that this individual was an almost perfect bed rest case during this period.

CONCLUSIONS

While a large number of our patients may be said to have shown some degree of improvement it is difficult to evaluate these findings. All of us are familiar with the psychosedative effects of any new drug in tuberculosis in which the patient goes through periods of hope and despair. The volumetric decrease in the sputum can well be due to the atropine-like effect of the antihistaminic drugs. On the other hand the excellent soporific effect of phenergan may also play a certain role. It is necessary for us to conclude then that in our limited experience the antihistaminic drugs whether alone or associated with streptomycin have not produced striking results in a trial of treatment of pulmonary tuberculosis. In this opinion we join the previous conclusions of the French investigators. An attempt will be made to choose a more select series for future investigation.

SUMMARY

1) The present knowledge of antihistaminics, particularly the pharmacologic considerations are presented.

2) Tuberculous allergy and tuberculous anaphylaxis are presented as widely different mechanisms and carefully differentiated.

3) Neo-Antergan and phenergan (RP3277) were given for several months in a series of thirty patients with tuberculosis. Although small changes in symptoms with slight improvement were noted in some cases, no definitive x-ray changes could be attributed to the use of these antihistaminics.

4) A further study using mainly cases with exudative lesions is planned.

REFERENCES

1 Fourneau, E. and Bovet, D.: "Recherches sur l'action sympathicolytique d'un nouveau derivé du dioxane," *Arch. internat. de pharmacodyn. et de therap.*, 46:178, 1933.
2 Lewis, T.: "The Blood Vessels of the Human Skin and Their Responses," London 1927 *(Shaw and Sons Ltd.)*.
3 Katz, G.: "Histamine Release in the Allergic Skin Reaction," *Proc. Soc. Exp. Biol. and Med.*, 49:272, 1942.
4 Bovet, D.: "La chemie des antihistaminiques," Rapport: II Congrés International de therapeutique, Bruxelles 1949.
5 Loew, E. R.: Rapport: II Congrés Intern. de Therap, Bruxelles 1949.
6 Corper, H. J.: Personal communication.
7 Dale, H. H. and Laidlow: "The Physiological Action of B Iminazolylethylamine," *Journ. Physiol.*, 41:318, 1910.
8 Rich, A. R.: "The Pathogenesis of Tuberculosis," p. 346-355 and 435-445. Published by *Charles C. Thomas*, Springfield, Ill., 1944.
9 Corper, H. J.: Personal communication and "Fundamental Information on the Mechanism of Specific Tuberculoimmunity," *Journ. Labor. and Clin. Med.*, 31:346, 1946.
10 Bauer, J.: "Veber Immunitaesvorgange bei der Tuberkulose," *Beitr. zur. Klin. der. Tuberk.*, 13:383, 1909.
11 Rolland, J.: Personal communication.
12 Vallery-Radot, Hamburger, J. and Halpern, B.: "Un nouvel antihistaminique de synthese," *Presse méd.*, 55:661, 1947. "Essais cliniques d'un nouvel antihistaminique de synthese derivé de la thiodiphenylamine," *Presse méd.*, 55:764, 1946.
13 Boquet, A.: "Substances antihistaminiques et réactions tuberculiniques," *Ann. Ins. Pasteur.*, 69:55, 1943.
Breton, A.: "Cuti-réactions a la tuberculine sur papules intradermiques de 2339 RP, antihistaminique de synthese," *Compt. rend. soc. de. biol.*, 137:254, 1943.
14 Guy, W. B.: "The Effect of Pyribenzamine on the Tuberculin Reaction in Man," *J. Invest. Dermat.*, 8:335, 1947.
15 Criep, L. H., Levine, M. I. and Aaron, Th. H.: "Inhibition of the Tuberculin Type Reaction by Antihistaminic Drugs and Rutin," 59:701, 1949.
16 Judd, A. and Henderson, A.: "Preliminary Report on the Use of Antihistaminic Drugs in Human Tuberculosis," Meeting of the American College of Allergists, April 15, 1949.
17 Wittich, F.: Discussion of the paper presented by Drs. Judd and Henderson.
18 Halpern, B. N. and Ducrot, R.: "Recherches experimentales sur une nouvelle serie chémique de corps doués de proprietés antihistaminiques puissantes; les derivés de la thiodiphenylamine," *Compt. rend. Soc. de. biol.*, 12:361, 1946.
19 Vallery-Radot, P., Blamoutier and Halpern, B. N.: Rapport: Congrés de la Soc. Franc. d'Allergie., 1948.

Antihistamines in the Treatment of the Common Cold: A Preliminary Report*

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So far as we can determine only three reports on the use of antihistamine drugs in the treatment of the common cold have appeared.[1,2,4] Our interest in them in the treatment of the common cold was stimulated by the report of Brewster in 1947 on the effect of diphenylamine hydrochloride (Benadryl) in over one hundred cases. Although at first we used various antihistamine drugs casually and without statistical analysis, we soon got the impression that in many patients the symptoms were modified and in a few instances the cold could be terminated within a few hours.

The present study was undertaken in an effort to carefully analyze the effect of these drugs. The patients were primarily medical students and student nurses on whom it was possible to maintain adequate observation and "follow-up." Because it was desired to interfere as little as possible with normal activity and work, and in order to best insure continuation of therapy, drugs known from previous experience to have few severe side effects were selected. A further element in the choice of drugs was to have tablets of approximately the same size and color.

Method of Study

Pyranisamine maleate (Neo Antergan†), and phenindamine (Thephorin††) were used in the study. Pyranisamine was given in 50 mgm. doses, phenindamine in 25 mgm. doses four times daily for three days. In some instances where rapid relief was obtained, patients found it unnecessary to complete a full course of therapy.

At first every other, later every third, patient was given placebo tablets which were of the same shape and color as the test drugs but without medicinal effects. They were given according to the same dosage schedule as the antihistamines. Patients receiving these tablets were used as controls.

The drugs and placebos were furnished in paper envelopes bearing only the dosage instructions and a code number. No patient was informed as to the drug or placebo that was used in his case.

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†Brand of pyranisamine maleate, supplied by Merck and Company.

††Brand of phenindamine, supplied by Hoffmann-La Roche, Inc.

TABLE I

	Total Cases	PYRANISAMINE			PHENINDAMINE			TOTAL ANTIHISTAMINE CASES			CONTROLS		
		Number Treated	Number Benefited	Per cent Benefited	Number Treated	Number Benefited	Per cent Benefited	Number Treated	Number Benefited	Per cent Benefited	Number Treated	Number Benefited	Per cent Benefited
Common Cold without Allergy	65	30	22	73	17	12*	71	47	34	72	18	8	44
Symptoms less than 12 hours	24	9	6	67	5	3	60	14	9	64	10	5*	50
Symptoms 12-24 hours	16	9	7*	78	4	4	100	13	11	85	3	1	33
Symptoms more than 24 hours	25	12	9†	75	8	5	63	20	14	70	5	2	40
Common Cold with Allergies (history)	27	6	6	100	10	8	80	16	14	88	11	5	45
Symptoms less than 12 hours	11	3	3†	100	3	3	100	6	6	100	5	3	60
Symptoms 12-24 hours	7	0	0	0	2	2	100	2	2	100	5	1	20
Symptoms more than 24 hours	9	3	3	100	5	3	60	8	6	75	1	1	100
TOTAL	92	36	28	78	27	20	74	63	48	76	29	13	45

* 1 case "aborted" † 2 cases "aborted"

The drugs and placebos were assigned in the order in which the patients presented themselves for treatment. Only those who came in complaining of a cold, with some symptoms of rhinitis: i.e. nasal congestion, nasal discharge, sneezing, burning, or itching of the nasal mucosa were accepted for the study. Although it is known that in many instances the first symptom of a cold may be a sore throat, patients with this only were excluded from the report. We felt that too many other conditions may be so manifested. However, a few of the patients were given one or another of the drugs with reported benefit.

Each patient filled out a form listing symptoms and their duration, the average number of colds per year and their average duration in the past, and any allergy history. In most cases the oral temperature and the appearance of the nasal and pharyngeal mucosa were recorded. Each patient was asked to return in 48 or 72 hours for further observation. The few that did not voluntarily return in the allotted time were seen the following day through the Student Health Service. At the time of return the forms were completed. This consisted in recording the time when relief of symptoms (if any) was obtained, the duration of symptoms, the time of treatment, and a subjective comparison of the present cold with previous ones as to severity and duration. Side effects attributed to the drug were noted. The nose and throat were usually not inspected if the patient was symptom free.

No attempt was made to interpret the statements made by patients comparing the duration and severity of their present cold with previous colds, since this was based upon subjective impressions and memory.

Results

A summary of the results obtained is given in Table I. For the purposes of evaluation, patients with histories of allergy were tabulated separately. Of the total treated with antihistamines 76 per cent were benefited with partial or complete relief of symptoms, whereas only 45 per cent of the control group reported such benefit. The type of benefit afforded was primarily disappearance of, or a decrease in, nasal congestion and/or nasal discharge. Others noted relief from cough, sore throat, sneezing, etc., but we did not consider these in the benefited group unless their nasal symptoms improved also.

Eighty-eight per cent of patients with history of allergy were benefited, as compared with 72 per cent of the non-allergy group. However, this was a small group, and the apparent difference may not be of real significance. Further, it was still impossible to predict which patient with allergies might be benefited. Finally,

it is in this group that there is the greatest difficulty in differentiating an acute cold from allergic rhinitis, and the results may be subject to some question on that account.

Colds were considered to be "aborted" only if symptoms were entirely relieved within 12 hours after the start of therapy and remained absent after treatment was discontinued. On this basis only seven colds could be considered as "aborted." Although a number of other patients stated that their colds were "aborted," some symptoms had persisted and therefore they were not included. Of the seven "aborted" colds, two had had symptoms for less than 12 hours, four from 12 to 24 hours, and one for a longer period.

Since we felt that it was extremely difficult, if not impossible, to determine the presence of a cold in patients whose symptoms were of less than three hours' duration, treatment was not given where symptoms had been present for a lesser period. At the other extreme, was the group who had had symptoms for more than 24 hours; in only a few of these were symptoms present for more than 48 hours. Two cases in this group were excluded from the tabulation because it was not possible to determine whether the clearing of symptoms was due to the effect of the drug or to the natural course of the cold. All other cases treated are included in this report.

There was no definite correlation between duration of symptoms prior to therapy and effectiveness of therapy, either as to relief of symptoms or number of colds aborted. A greater percentage with symptoms of 12 to 24 hours' duration were relieved than either of the other groups, but here again this series was small, and statistical significance may be lacking. Further breakdown of the small group (20) whose symptoms had been present less than 12 hours likewise showed no correlation between results of treatment and duration of symptoms.

TABLE II
Side Effects

	Drowsiness	Insomnia	Nervousness	Vertigo	Weakness	Headache	Dry Mouth	Total Cases with Side Effects	Per cent of Cases Treated
Pyranisamine maleate	6	1	.	2	.	1	4	13*	39
Phenindamine	1	4	.	.	1	.	1	7	26
Controls	1	.	1	1	.	.	.	3	10

* More than one side effect reported by one patient.

The principal side effects reported for each drug are recorded in Table II. Only one patient complained of more than one side effect. It is of interest to note that one patient receiving a placebo complained of numbness and tingling in the hands. For the most part the side effects were not severe, and in no instance was a drug discontinued because of them.

Discussion

The results reported here show a much smaller percentage of patients benefited than in the series reported by Brewster,[2] or Gordon.[4] Although treatment was not initiated in any case with symptoms for less than three hours, we did not observe any definite correlation between duration of symptoms and benefits obtained, including "aborted colds." Patients with a history of allergy of some type were benefited in a higher percentage than the others.

There was no significant difference between results from pyranisamine maleate and phenindamine. Although the former gave a higher percentage of side effects, none was severe enough to interfere with therapy. Results in the control group, although small in number, were similar to those obtained in other investigations of the common cold, particularly efforts to prevent colds, such as those of Cowan, Diehl and Baker.[3]

Although our results are not startling, it appears that there was a definite and significant difference in the percentage of cases benefited with antihistamine therapy, as compared to the control group. While no attempt at analysis was made, it may be that those cases that fail to benefit, or those that have a recurrence of symptoms after therapy is stopped, should be re-evaluated, particularly with reference to possibility of infection of the paranasal sinuses.

We do not claim, as a result of this investigation, that there is an altered response to viral or bacterial infection, but rather that there may be a modification of symptoms. A possible rationale for the use of the antihistamines in the manner here reported is suggested by the report of Troescher-Elam[5] and co-workers, who noted the presence of a histamine-like substance in nasal secretions from patients with the common cold, in quantities at least equal to that from patients with allergic rhinitis.

SUMMARY AND CONCLUSIONS

1) Sixty-three cases of the common cold were treated with antihistamines and 29 with placebos as a control.

2) There appeared to be a definite and significant percentage of cases benefited by the antihistamines.

3) Few colds seemed to be truly "aborted" by this therapy.

4) Neither duration of symptoms of a cold nor a history of allergy is any indication of the amount of benefit that may be expected.

5) The results obtained in this small series warrant further critical investigation and study.

SUMARIO Y CONCLUSIONES

1) Sesenta y tres casos de catarro común fueron tratados con antihistaminas y 29 con "placebos" como testigos.

2) Parece que hay un porcentaje definido y significante de casos beneficiados por los antihistamínicos.

3) Pocos catarros parecen haber sido verdaderamente "abortados" por esta terapéutica.

4) Ni la duración de los síntomas, ni los antecedentes de alergia en un caso de catarro común, son indicadores del grado de beneficio que es de esperarse.

5) Los resultados obtenidos en esta pequeña serie autorizan a una investigación ulterior y estudio crítico.

REFERENCES

1 Brewster, John M.: "Benadryl as a Therapeutic Agent in the Treatment of the Common Cold," *U. S. Naval Med. Bull.*, 47:810, 1947.
2 Brewster, John M.: "Antihistamine Drugs in the Therapy of the Common Cold," *U. S. Naval Med. Bull.*, 49:1, 1949.
3 Cowan, D. W., Diehl, H. S. and Baker, A. G.: "Vitamins for the Prevention of Colds," *J.A.M.A.*, 120:1268, 1942.
4 Gordon, John S.: "Antihistaminic Drugs in the Treatment of Upper Respiratory Tract Infections," *Laryngoscope*, 58:1265, 1948.
5 Troescher-Elam, E., Ancona, G. R. and Kerr, W. J.: "Histamine-Like Substance Present in Nasal Secretions of Common Colds and Allergic Rhinitis," *Am. Jour. Physiol.*, 144:711, 1945.

The Effects of Administration of Protein Hydrolysate (Amigen), Testosterone and Folic Acid on Nitrogen Balance in Patients with Chronic Pulmonary Tuberculosis*

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Although extensive work[1-8] has been done on the nutritive value of intravenous alimentation with amino acids for relatively short periods of time in acute medical and surgical problems, little, however, has been reported in chronic disease states. Elman and Wiener[9] were among the first to extensively study in patients the intravenous use of animo acids. They found amino acid therapy of value in malnutrition and in the prevention of postoperative starvation. Confirmation of the beneficial effects of parenteral use of amino acids has been reported by other investigators.[10-17] Farr,[18] in studies on nephrotic children, reported that positive nitrogen balance may be obtained with the injection of enzymatic hydrolysates providing about 5 per cent of the total nitrogen intake.

The purpose of the present study was to investigate alterations in nitrogen storage following administration of protein hydrolysates in patients with a chronic wasting disease such as pulmonary tuberculosis or ulcerative colitis. In addition, it seemed desirable to determine the efficacy of testosterone and folic acid as dietary supplements in promoting nitrogen retention.

Materials and Methods

Five patients with chronic pulmonary tuberculosis and one with chronic ulcerative colitis were intensively studied to ascertain the effect of intravenous administration of protein hydrolysates. Three of the 5 tuberculous patients were in good nutritional state and in nitrogen equilibrium, the other two, as well as the patient with ulcerative colitis, were in poor nutritional state in negative nitrogen balance.

The patients selected were hospitalized for many months to provide a base-line period. The weight and general condition of

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each patient were closely followed throughout the experiment, and laboratory studies were reported at frequent intervals. The observation periods varied from four to 18 months and included successive cycles of control and therapy periods.

The source of amino acids used in this investigation was Amigen,*[19] a hydrolysate of casein made by enzymatic digestion of pork pancreas. The periods of Amigen administration were from one to eight weeks and the dose was 1,000 cc. or 2,000 cc. of 5 per cent Amigen.* Finally, periods of testosterone** and folic acid*** therapy with or without Amigen were studied for comparison. Daily intramuscular injections of 25 mgms. of testosterone and 10 mgms. of folic acid for five days for each week were employed.

These patients were under the direction of a specially trained graduate nurse during the period of study. A dietician was in charge of the kitchen where the food was accurately weighed and the menus planned to the palate of each patient. The daily caloric and nitrogen intake was computed from Sherman's[20] Tables with allowances made for uneaten food which was carefully weighed.

All urine and stool specimens were collected throughout the 24 hour period. Total 24 hour urinary outputs were preserved with toluene and pooled for a six day period. The daily urine specimens were analyzed for creatinine[21] as a check on the adequacy of the collection of the specimens. Urine specimens in which the creatinine figures were too low were discarded as inadequately collected and were not pooled. The total urinary nitrogen output was determined from the pooled specimens by the gasometric micro-Kjeldahl method[22] and computed on a 24 hour basis.

The stools were collected daily, preserved with 500 cc. of 10 per cent sulfuric acid and pooled for a six day period. The pooled specimens were weighed and homogenized by vigorous stirring for one hour with an electric mixer. A weighed sample of 10 to 15 gms. was then dissolved by heating with concentrated sulfuric acid, cooled and made up to a known volume. A suitable amount was sampled for analysis and the nitrogen determined as for the urine.

Nitrogen balances were calculated from the data tabulated for the total nitrogen intake and total nitrogen excretion.

Plasma volume studies were made using the dye T 1824.[23] The serum proteins as well as their fractions (including the three globulin groups) were chemically determined.[24] The total circulating plasma protein was then calculated from these data.

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*Amigen for this experiment was liberally supplied by Mead Johnson and Company.

**Testosterone propionate was furnished through the courtesy of the Ciba Company.

***Folic Acid was supplied as "Folvite" by the Lederle Laboratories.

Results

The experiment was divided into control and experimental periods. The first control period of two to five weeks was followed by a period of intravenous administration of Amigen for two to six weeks. Similar successive control and treatment cycles followed. During these alternating phases the amount and length of periods of Amigen treatment varied. The daily dose of Amigen was usually 1,000 cc. given five days a week, but at other periods 2,000 cc. were employed. Periods of Amigen combined with testosterone and folic acid followed the periods of Amigen therapy alone, and lastly periods of testosterone and folic acid without Amigen were studied for comparison.

Patient No. 1 (H.W.) M.H. No. 40749: This 44 year old white male complained of fatigue and weight loss of 25 lbs. in August 1943. He was admitted to Montefiore Hospital on May 19, 1944, where a diagnosis of bilateral fibrocaseous tuberculosis was made. The sputum was positive for tubercle bacilli but was negative after February 5, 1945. Radiographic examination revealed numerous nodular densities throughout the upper one-third of the left lung. The right upper lobe was obscured by a density which was sharply delimited by the horizontal fissure and there were several nodular densities scattered throughout the right mid-lung field. On bedrest he gained 16 lbs. and on semi-ambulant care he continued to gain an additional 24 lbs. His nutritional state was good when he came to the metabolic wards for treatment with Amigen. During treatment for one year, he gained another 5 lbs. On discharge from the hospital, his x-ray films revealed clearing of the previous infiltrations.

The findings on this patient (No. 1) during the control and experimental periods are shown in Chart 1. From these it appears that during periods one to 10 no marked nitrogen retention was obtained. In periods 21 to 64 the mean nitrogen balance varied from plus 5 to plus 11 gms. in 24 hours. The explanation for this observation may be found in the influence of ambulation on nitrogen balance.[25] In the beginning of the experiment the patient was confined to bed during the period of Amigen administration but was allowed to be ambulatory during the control period. In the latter part of the experiment the patient was ambulant during the Amigen as well as during the control period. Nitrogen balance increased in this patient when testosterone was given with Amigen, but this response was not as marked as in other patients. Folic acid with testosterone produced a positive nitrogen balance during the one period in which it was studied.

A tendency for the total circulating protein and body weight to rise during Amigen administration when the patient was in positive balance and to fall again during the control periods was observed. The rise in total circulating protein was probably partly

due to an increase in plasma volume as well as in plasma protein concentration.

Patient No. 2 (N.R.) M.H. No. 39256: The onset of illness in this 35 year old white male occurred in 1935. The sputum was positive for tubercle bacilli and x-ray examination revealed tuberculosis of the right lung. After induction of artificial pneumothorax, the sputum became negative. In 1943 he had several small hemoptyses and was admitted to Montefiore Hospital. His sputum again became positive for tubercle bacilli. X-ray films at this time showed the right lung to be fibrotic with a thickened

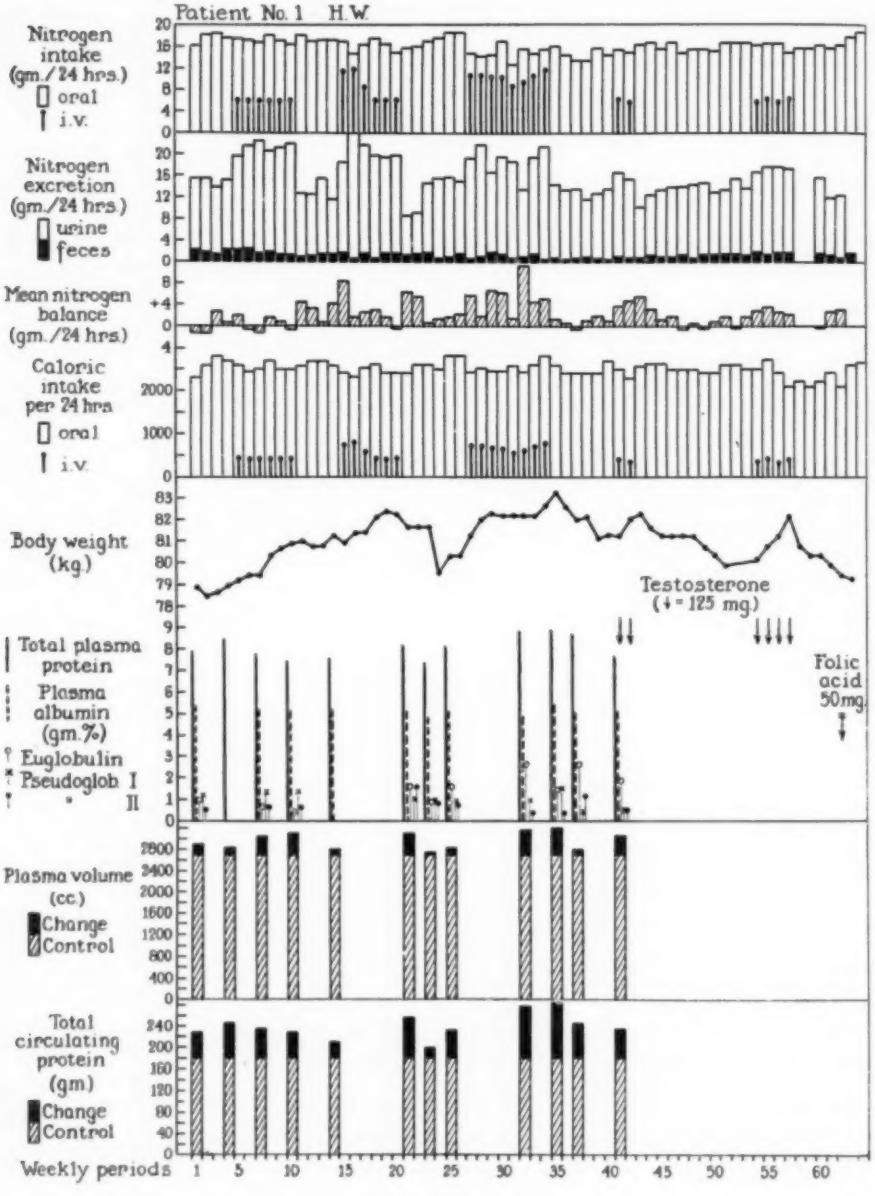

CHART 1

pleura. The left lung had numerous infiltrations in the upper portion with at least two large cavities. He was transferred to the metabolic ward for treatment with Amigen. However, his disease progressed steadily and he expired on September 27, 1945.

The observation periods on this patient (No. 2) were short as illustrated in Chart 2. The first reliable laboratory studies available are for the period of Amigen administration when the nitrogen balance was plus 4.24 gms. per 24 hours. During the six week control period the nitrogen balance fell to plus 1.23 gms. During both the Amigen and control periods the patient was confined to bed. Because this patient was studied for a relatively short period, no conclusions could be drawn as to the effect of therapy.

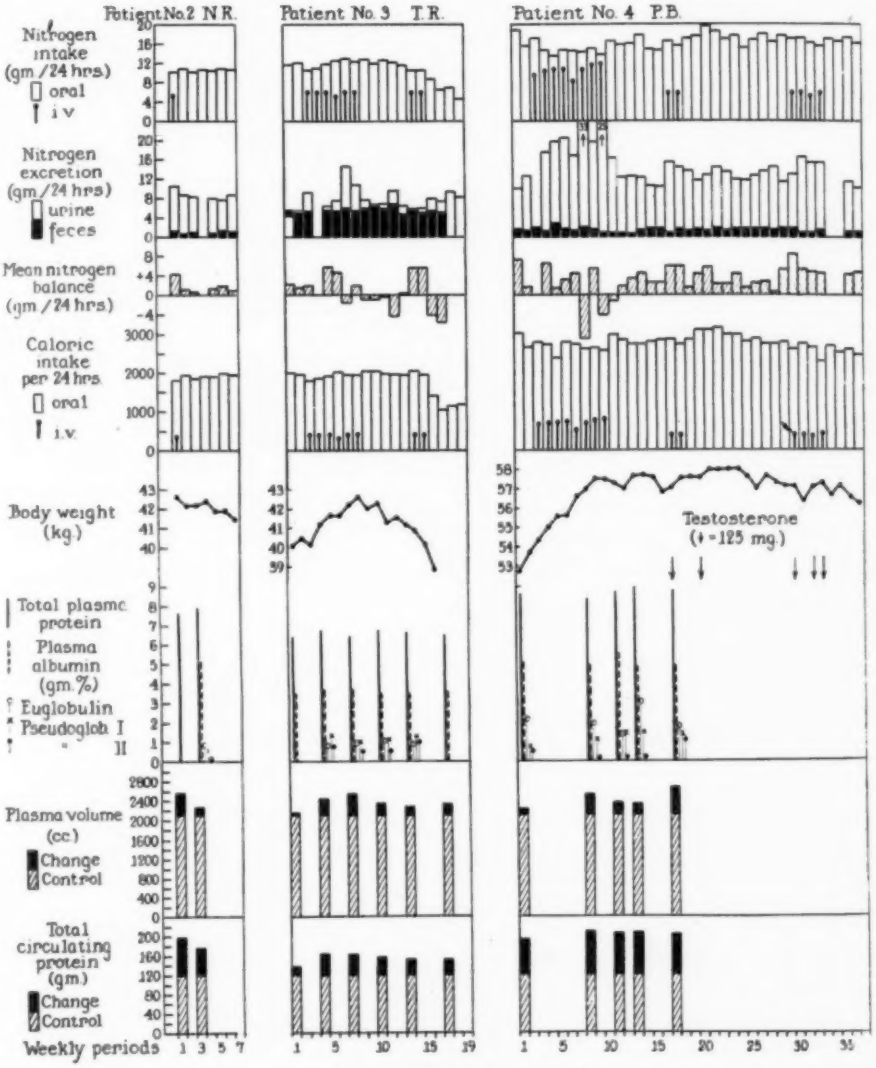

CHART 2

Patient No. 3 (T.R.) M.H. No. 37448: After several admissions to other hospitals because of diarrhea, a 17 year old white male entered Montefiore Hospital on September 17, 1943 with the complaint of diarrhea and fever. A diagnosis of non-specific colitis was made. Under intravenous Amigen therapy, the patient gained 30 lbs. in three months. He was discharged but readmitted shortly thereafter in November 1944 with an exacerbation of symptoms. On admission the dietary regimen was carefully supervised and large doses of Amigen were given. The patient developed persistent watery stools, became moribund and died on July 31, 1945.

When this patient was observed for a preliminary two week period, the nitrogen balance was found to be plus 1.85 gms. per 24 hours. For the next six weeks Amigen was given with a consequent rise of positive nitrogen balance to 2.51 gms. per 24 hours; but during the control period which followed, the nitrogen balance fell to minus 1.31 gms. per 24 hours. When the Amigen was resumed, the positive nitrogen balance again rose to plus 5.69 gms. per 24 hours but changed to a negative balance, minus 5.02 gms. per 24 hours, when discontinued. During the experiment, the patient remained in bed.

The patient lost large amounts of nitrogen in his stool because of diarrhea. During the periods of Amigen administration, nitrogen excreted in the stools remained unchanged while the nitrogen excreted in the urine increased, but was less than the amount of nitrogen intake with a consequent result that the nitrogen balance increased.

The data on patient (No. 3) presented in Chart 2 revealed that the nitrogen retention was more marked when Amigen was administered after a period of negative balance than when it was given following an initial period of a positive nitrogen balance. The body weight rose from 40.1 kg. to 42.6 kg. during the 6 week Amigen period. The plasma volume rose from 2,100 cc. to 2,500 cc. and the total circulating protein rose from 137 to 162 gms. during the same period, while the concentration of total proteins remained unchanged.

Patient No. 4 (P.B.) M.H. No. 40646: A white male aged 25 years rejected for military service in October 1942 because of pulmonary tuberculosis was admitted to Montefiore Hospital on April 3, 1945. In December 1944 his sputum was positive for tubercle bacilli and x-ray examination revealed extensive bilateral pulmonary disease with cavitation in both upper lobes. Bilateral artificial pneumothorax was attempted and abandoned after a brief period because it was technically ineffective. Clinically and radiographically there was evidence of progression of his disease and he left the hospital against advice.

During the first week of a control period, patient (No. 4) was ambulatory, and the nitrogen retention was plus 4.4 gms. per day

(Chart 2). In the following eight weeks 2,000 cc. of Amigen were given daily and the patient remained in bed most of the day. During this period, the nitrogen retention balance remained unchanged. Amigen combined with testosterone was given for two weeks following a second control period; a marked rise in the nitrogen retention to plus 6.02 gms. per day was noted but fell to plus 1.71 gms. per day during the first week of the following control period.

On testosterone alone, for a period of one week following this control period, the nitrogen retention again reached plus 4.44 gms. per day and remained so for the next four weeks. For this latter four week period, the patient was on diet alone and his nitrogen balance was plus 3.7. Part of the positive nitrogen balance was probably a carry-over effect from the testosterone therapy.

A five week control period, following one week intermission, revealed that the nitrogen retention fell to plus 2.53 gms. per day. Amigen with testosterone was administered for a two week period and the nitrogen retention rose to 7.02 gms. per day. When Amigen alone was again given for a two week period, the nitrogen retention fell to plus 4.81 gms. per day. The caloric intake also dropped off in the second week. After a four week control period the nitrogen retention still remained at 4.64 gms. per day.

This patient showed an increase in plasma volume of 12 per cent and in total circulating protein of 10 per cent following eight weeks of double dose Amigen administration. The body weight rose from 54.4 kgs. to 58 kgs. during the same period. Graphic representation of the study on this patient is given in Chart 2.

Patient No. 5 (P.H.) M.H. No. 48496: A 26 year old white male was hospitalized in 1933 because of severe hemoptysis. Sputum was found to be positive for tubercle bacilli and fibrocaseous tuberculous involvement was demonstrated by x-ray film in the left lung. Artificial pneumothorax was attempted but discontinued because of obliterative pleuritis. Several small hemoptyses occurred and a contralateral lung lesion appeared. Pneumothorax was also attempted on this side and was abandoned because of the development of pleural effusion. A three stage thoracoplasty on the right side was completed in May 1943.

His sputum remained positive for tubercle bacilli and the lesion in the left lung was steadily progressive in spite of strict bedrest during the entire hospital stay. During the time he was receiving Amigen, he had elevations in temperature and a cough which induced vomiting. Serial roentgenograms revealed slow, steady progression of his disease with bilateral cavitations. He died December 15, 1946.

From Chart 3, patient No. 5, it can be seen that during the initial four week control period, this patient showed a negative nitrogen balance in spite of adequate caloric and nitrogen intake. Administration of 1,000 cc. of Amigen daily for six weeks resulted in nitro-

gen equilibrium. This was maintained during the subsequent five weeks on diet alone. Amigen given for four weeks further increased nitrogen retention to plus 1.5 gms. per day. During the following three weeks, when the patient received diet alone, the nitrogen balance remained at plus 1.47. A long Amigen period of eight weeks followed during which the nitrogen balance fell to equilibrium. The oral caloric intake dropped and the patient was intermittently febrile and had a cough associated with vomiting during

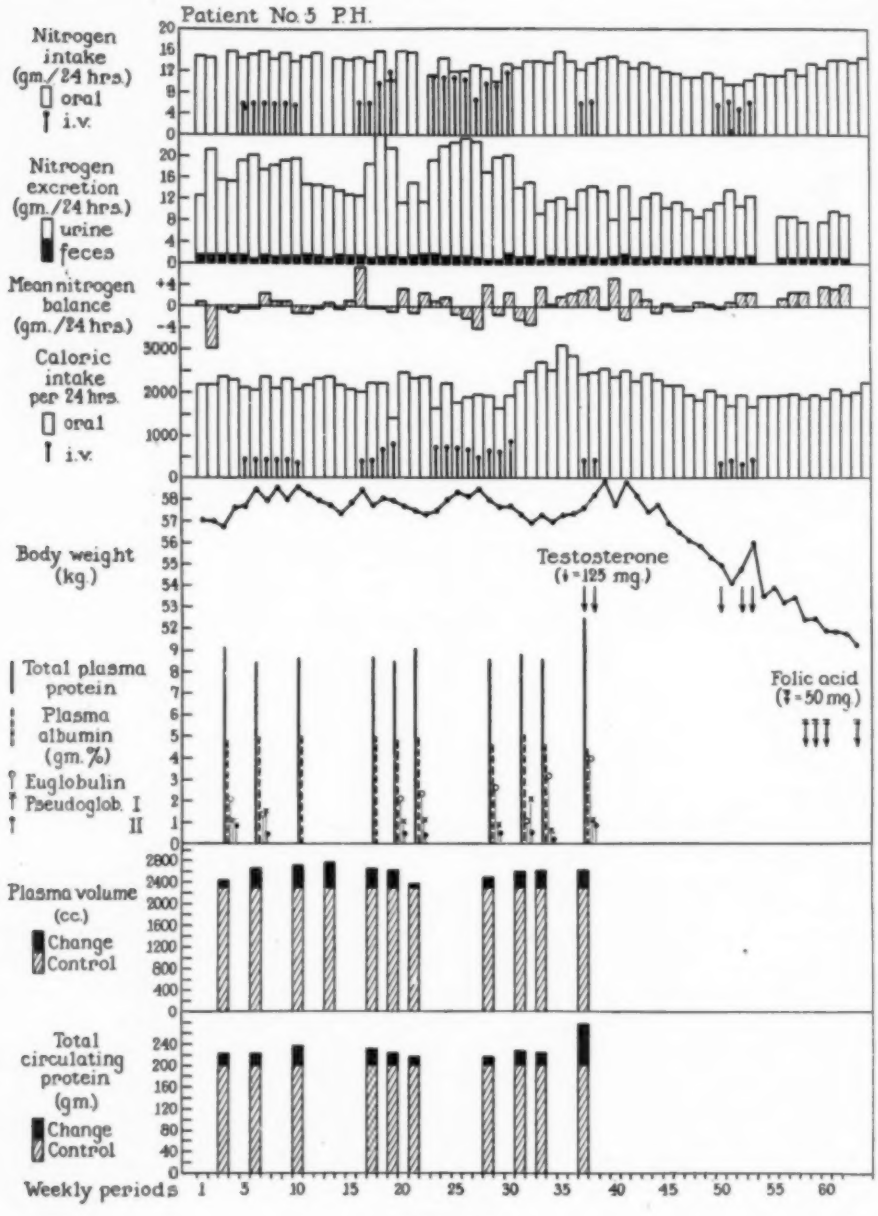

CHART 3

this period. The nitrogen equilibrium of this period was maintained for the following six weeks on diet alone.

For the next two weeks Amigen and testosterone produced a positive nitrogen balance of 3.34 gms. per day which reached equilibrium during the following week when all therapy was discontinued. Nitrogen retention of 5.15 gms. per day developed in the next week when testosterone without Amigen was resumed. This receded again promptly upon the cessation of therapy. The patient was in nitrogen equilibrium during this control period of nine weeks as well as in the following two week period of Amigen therapy. When testosterone and Amigen were again given for another four week period, the nitrogen balance again became positive at plus 2.32 gms. per day. In the following control period of two weeks, nitrogen retention of plus 1.87 gms. per day was maintained but increased to 3.1 gms. per day during the next three weeks when folic acid was given intramuscularly. A carry-over effect was noted during the next two weeks when the nitrogen balance remained at plus 3.61 gms. per day on diet alone.

In this patient with active progressive tuberculosis Amigen produced a retention of nitrogen only early in the experiment when the nitrogen balance was positive or near equilibrium. Testosterone and folic acid both produced a marked positive nitrogen balance when given alone or with Amigen.

During the early months of the experiment, the patient was partially ambulant. However, during the latter part he became progressively worse and remained in bed during the period when Amigen was employed. Episodes of fever, chills, and vomiting occurred during and following Amigen infusion.

In this patient (No. 5) in an earlier period, before the disease became progressive, the use of Amigen was accompanied by a moderate increase of weight up to 2 kgs. which fell to the initial level during the control periods. Later when his disease became progressive, he lost steadily in body weight irrespective of Amigen with or without testosterone and folic acid. The total caloric intake during the early experimental period remained at a constant level of about 2,500 calories. During the Amigen administration, the oral caloric intake decreased but the total was maintained by intravenous alimentation. In the latter part of the study, the total caloric intake decreased irrespective of treatment with Amigen, testosterone or folic acid. The plasma volume showed an increase of 10 per cent following the first period of Amigen administration and decreased slightly during the second control period. This again rose following the next period of Amigen.

Patient No. 6 (P.P.) M.H. No. 42482: A 32 year old white male first noted weight loss and fatigue in January 1940. His sputum was found to be

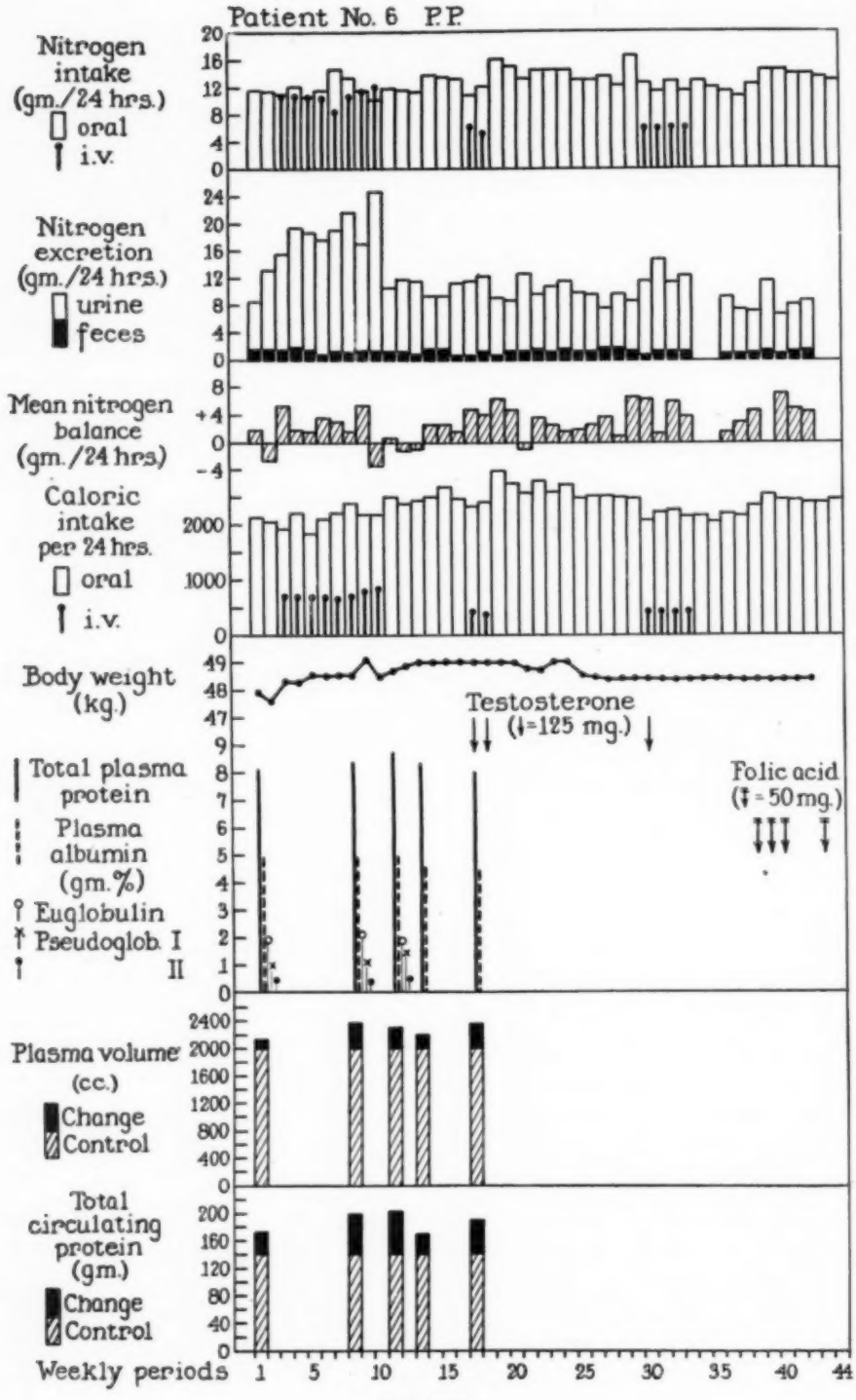
Patient No. 6 P.P.
Nitrogen intake (gm./24 hrs.)
oral
i.v.
Nitrogen excretion (gm./24 hrs.)
urine
feces
Mean nitrogen balance (gm./24 hrs.)
Caloric intake per 24 hrs.
oral
i.v.
Body weight (kg.)
Testosterone (↓=125 mg.)
Folic acid (↓=50 mg.)
Total plasma protein
Plasma albumin (gm.%)
Euglobulin
Pseudoglob. I
II
Plasma volume (cc.)
Change
Control
Total circulating protein (gm.)
Change
Control
Weekly periods
1 5 10 15 20 25 30 35 40 44

CHART 4

positive for tubercle bacilli at another hospital and the disease was progressive in the right lung, with a large cavity in the mid-lung field. Treatment with artificial pneumothorax supplemented by phrenic crush failed to control the progress. In June 1945, he was admitted to Montefiore Hospital because of profuse hemoptysis. The radiographic examination revealed infiltrations in the apical portions of the left lung with cavity formation. The right lung had fibrotic infiltrations scattered throughout with a large cavity in the upper lobe. Three ounces of sputum were expectorated daily. Bedrest and a high protein diet which was supplemented by intravenous Amigen were employed for therapy. His disease progressed gradually and he died on May 26, 1947.

This patient (No. 6, Chart 4) was observed for a two week control period during which he was found to be in nitrogen equilibrium. This was followed by an eight week period of Amigen treatment at which time a positive nitrogen balance of 2.61 gms. per day was obtained. Following the control period of six weeks, he returned to nitrogen equilibrium.

When Amigen plus testosterone were given during the next two week period, a positive nitrogen balance of 4.41 gms. per day was obtained although only half the previous dose of Amigen was injected. A marked carry-over effect was noticed the next week when neither Amigen nor testosterone was given; and this was maintained for the following week on testosterone alone. However, during the succeeding four week control period the nitrogen balance returned as before toward the control level.

After an intermission, the patient was observed for another five week control period, during which a positive nitrogen balance of 3.12 gms. per day was obtained. The increase in nitrogen retention may be explained by the fact that immediately preceding this control period, the patient developed a rectal fistula which confined him to bed. When the fistula began to drain, he was allowed to be ambulant again. The resumption of ambulation[25] and clearing of infection[26,27] may have contributed to the increase in nitrogen storage. However, administration of testosterone plus Amigen resulted in an elevation of nitrogen balance to plus 4.91 gms. per day. The nitrogen balance dropped to plus 2.14 gms. per day when Amigen and testosterone were discontinued, and again rose to an even higher level of plus 5.78 gms. per day during the next three week period of folic acid administration. A carry-over effect was again observed during the next two weeks on diet alone, the nitrogen balance averaging plus 4.45 gms. per day.

It would seem from these data on this patient that Amigen administration increased the nitrogen retention when the nitrogen balance was close to equilibrium but had no noticeable effect when the nitrogen balance was originally positive. However, both

testosterone and folic acid caused further nitrogen retention even when the nitrogen balance was already strongly positive.

Total circulating protein increased from 170 to 200 gms. following the eight week period when 2,000 cc. of Amigen were given daily, and then fell again to 169 gms. during control periods. This rise was due largely to an increase in the plasma volume of more than 20 per cent. Throughout this period there was an increase of body weight of 1.6 kgs.

Discussion

Nitrogen equilibrium is said to exist when the nitrogen intake is equal to the nitrogen excretion. If depletion of tissue protein occurs more rapidly than its replacement, a negative nitrogen balance results. Individuals in the depleted state will retain about 30 gms. of protein to replenish the tissues for every gram of plasma protein formed.[28] Subjects in good nutrition, with their protein stores saturated, can be maintained in nitrogen balance by a relatively small daily intake of protein if enough calories are ingested.

From Chart 1 in patient No. 1, it is to be noted that this individual was in good nutritional state and in nitrogen equilibrium at the commencement of the experiment. During subsequent periods of treatment, there was a slight increase in the nitrogen intake due to administration of protein hydrolysate intravenously which produced an increase in nitrogen balance, except in the first period of treatment. During control periods when no intravenous therapy was administered on a constant oral intake of nitrogen, the patient maintained his positive balance.

It has been found that in patients in poor nutritional condition[29-33] and showing an initial negative balance, improvement in nitrogen balance is more rapid and pronounced; this observation was confirmed in the present study. It can be seen in Charts 2, 3 and 4 that patients 2, 3, 5 and 6 were in poor nutritional state and in or near negative balance at the commencement of the experiment. During subsequent periods of treatment, it can be noted that the additional nitrogen intake, chiefly derived from intravenous administration of hydrolysates, increased the nitrogen balance considerably in a brief period of time. However, during the control period there was a marked drop to a negative nitrogen balance.

In these same patients, studied during a period of nitrogen balance, the treatment and control periods no longer showed wide fluctuations. This is not surprising and is in accordance with the observation of Peters[27] who has emphasized the ability of the poorly nourished individual to conserve protein and attain nitro-

gen equilibrium in conditions under which the better nourished individual fails. He suggests that the synthesis of protein may vary inversely with the state of nutrition. Some earlier observations[81] on nephrotic children also pointed to the relationship between ability to store proteins in partial starvation and the patient's nutritional condition.

The variability of nitrogen retention is known to be related to many factors which influence nitrogen storage, such as, ambulation,[25] nutritional status, infection, fever and diarrhea.[26,27] These factors are thought to lead to increased catabolism of the protein or an abeyance in the protein synthesis.[34,35]

In patients No. 1, 4 and 5 during some periods of Amigen administration, there was a fall of nitrogen retention while during most other periods there was a definite increase of nitrogen retention as compared to the control periods. The fall in nitrogen retention could be explained in two patients, No. 4 and No. 5, by the fact that they were febrile at the time and showed evidence of active tuberculosis. They also showed occasional reactions to the intravenous injections of hydrolysate by severe chills, fever, anorexia and vomiting. It is well known that under conditions of tissue damage and infection, amino acids are not utilized but deaminized and excreted as urea.[27]

Patient No. 1 who had a positive nitrogen balance and was in good nutritional state before the administration of Amigen, showed a decrease in nitrogen storage during the first period of treatment with Amigen. This paradoxical effect can probably be explained by the influence of bedrest and ambulation on nitrogen balance. The increased output of nitrogen due to the immobilization of this patient during the first phase of this experiment might have obscured the effect of Amigen on nitrogen storage. Later in the experiment when the patient remained ambulant during Amigen administration, the expected effect on nitrogen storage was observed.

Normally, the ratio of nitrogen excretion in the stool and urine is about 1:10. The ratio is shifted in favor of increased nitrogen excretion in the urine during Amigen administration. In patient No. 3 with frequent diarrhea, the ratio of nitrogen excretion in the stools and urine was about 1:1. In this instance, administration of Amigen tended to reverse the nitrogen excretion in the urine towards the normal ratio. These findings are in accord with results of other authors.[9]

Computed as average values for periods of one or several weeks, the increase of nitrogen output was, as a rule, somewhat smaller than the increase of nitrogen intake during periods of Amigen administration. This resulted in a more positive nitrogen balance

which varied with each patient and also in the same patient during different phases of the experiment. From Chart 1 it can be noted that Amigen administration in patient No. 1, who was in good nutritional state and in positive balance at the commencement of the experiment, resulted in nitrogen retention of 0.2 gms. to 5.3 gms. per 24 hours during the six week period. In patient No. 6 who was in poor nutritional state and in negative balance at the commencement of the experiment, the nitrogen retention during Amigen administration varied from 2.6 to 3.8 gms. per 24 hours during the period.

Testosterone propionate in daily doses of 25 mg. caused marked nitrogen retention. In patients No. 1, 4, 5 and 6, who received this androgen, the increase of nitrogen retention was between 3 and 5 gms. per 24 hours. These findings are in accordance with the well established effect of testosterone propionate.[36-38] It has been observed by different workers that when patients are given a constant nitrogen intake, the administration of testosterone propionate caused a decrease in the urinary nitrogen with no appreciable change in the fecal nitrogen, so that increased amounts of nitrogen are retained. These changes are apparent by the 2nd or 3rd day and reach their maximum between the 5th and 15th day. In our patients, the nitrogen retention was still seen for some time after testosterone had been discontinued. Furthermore, nitrogen retention caused by Amigen was more pronounced when testosterone was added.

The combined use of folic acid[39] and Amigen caused a definite but temporary increase of nitrogen balance in the three patients who received this form of treatment. This experiment confirms the nutritive value of folic acid as pointed out in the literature.

From these experimental data it appears that the use of protein hydrolysates with or without the addition of testosterone or folic acid corrected the nitrogen imbalance in patients with chronic wasting disease.

Several investigators[40,41] have studied the utilization of parenterally administered amino acids under varying conditions of total caloric and carbohydrate intake. Schwimmer[42] concludes that nitrogen balance is not maintained when dietary protein or hydrolysate is not supplemented with adequate caloric intake. Some evidence in man suggests that the injection of amino acids without glucose results in a greater excretion of nitrogen in the urine than when glucose is added. The data indicate that when the daily caloric intake is only 800 calories, nitrogen balance is not achieved, but on an intake of 1,200 calories this can be obtained.[40,41] The importance of a high caloric intake in maintaining positive

nitrogen balance in convalescence has been confirmed by recent reports.[26,27]

In all of our patients, the diet was high in carbohydrate and glucose was present in the solution of the protein hydrolysate given parenterally. The caloric intake in these patients was never less than 2,000 and ranged as high as 3,500 calories. Food intake was generally decreased, especially when daily doses of Amigen were given intravenously or in case of febrile reactions caused by disease. In patient No. 1, who had quiescent pulmonary tuberculosis with negative sputum and was afebrile, Amigen administration in 2,000 cc. doses did not decrease the food intake. However, in patient No. 5, with extensive bilateral disease, an active and progressive course with fever and positive sputa, there was a decrease in food intake from the daily average of 2,400 calories during the administration of single doses of Amigen to approximately 1,800 calories during the administration of double doses of Amigen. In the patients No. 4 and 6, who also had active and progressive tuberculosis, there was a similar decrease in food intake when double doses of Amigen were injected.

The average plasma volume during the periods of Amigen administration was 3,087 cc. in patient No. 1 in contrast to the control volume of 2,908 cc. In patient No. 3 the average plasma volume was 2,393 cc. during Amigen administration and 2,316 cc. during oral nitrogen intake. In patient No. 4, the plasma volume during Amigen administration was 2,602 cc., during oral intake 2,301 cc. Patients No. 5 and 6 showed only slight differences in the plasma volume figures in favor of the intravenous nitrogen route. We are aware of the rather wide range of experimental error in plasma volume determinations, but since we have observed consistent changes, we deem them to be worthy of note.

Concomitantly with the increase in total plasma volume, there was an increase in total circulating protein due largely to the former because the serum protein concentration did not show any rise. There were no consistent changes in the individual protein fractions. The lack of marked serum protein changes is in accordance with the established fact[28] that over 96 per cent of the nitrogen retained is utilized for the replenishment of the tissue protein.

Cannon[43] has recently pointed out the relationship between protein reserves and antibody production. We began our study originally in an attempt to determine whether prolonged administration of amino acids would have any influence in altering the course of chronic infectious disease. While we realize fully that the interpretation of possible clinical changes is exceedingly difficult in a study of this sort, we have come to the conclusion that

the administration of protein hydrolysate intravenously did not alter the course of the underlying pathological state even though it did correct the nitrogen balance.

SUMMARY

1) Nitrogen balance studies were made on six patients with chronic wasting disease. Five of them had chronic pulmonary tuberculosis; three were in positive and two in negative nitrogen balance at the start of the experimental period. The sixth patient had non-specific ulcerative colitis and was also in negative nitrogen balance. Periods of therapy with Amigen, testosterone and folic acid alone or in combination, were alternated with control periods for comparison as to the effect on the course of the disease when patients were in negative and positive nitrogen balance.

2) When patients were at bedrest, Amigen administration did not increase the nitrogen as markedly as when they were ambulant, Amigen improved the nitrogen balance.

3) During periods of activity of the disease, the use of Amigen did not as a rule increase the nitrogen balance. The degree of nitrogen retention during Amigen administration varied inversely with the degree of nitrogen and nutritional deficiency at the time.

4) Folic acid or testosterone increased nitrogen retention more than Amigen alone.

5) Increase in plasma volume and total circulating proteins was frequently seen following proportional to the increase in nitrogen retention.

6) The disease state was not altered by the intravenous administration of protein hydrolysate although the nitrogen imbalance was corrected by the parenteral administration of Amigen.

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RESUMEN

1) En seis enfermos con enfermedades crónicas debilitantes se hizo el estudio del equilibrio nitrogenado. De ellos, 5 tenían tuberculosis pulmonar crónica; tres estaban en equilibrio positivo nitrogenado y dos negativos al principio del periodo experimental. El sexto enfermo tenía una colitis ulcerosa no específica y su equilibrio nitrogenado esta también negativo. Se alternaron periodos de uso del Amigen, testosterona, y ácido fólico solos o en combina-

ción con periodos de control para comparar el efecto de los equilibrios positivo y negativo nitrogenados sobre la evolución de la enfermedad.

2) Cuando los enfermos permanecieron en cama la administración de Amigén no aumentó la retención de nitrógeno, pero cuando deambulaban el Amigen mejoró el equilibrio nitrogenado.

3) Durante periodos de actividad de la enfermedad el uso de Amigén no aumentó el equilibrio nitrogenado. El grado de retención de nitrógeno mientras se usó el Amigén varió de modo inverso con el grado de deficiencia nutritiva y nitrogenada en ese tiempo.

4) El ácido fólico o la testosterona aumentaron la retención de nitrógeno más que el Amigén solo.

5) El aumento de volumen del plasma total y las proteínas circulantes totales, fué proporcional al aumento de la retención de nitrógeno.

6) El estado de la enfermedad no fué alterado por la administración de hidrolisado de proteínas, aunque el desequilibrio nitrogenado fué corregido por la administración parenteral del Amigén.

REFERENCES

1 Rose, W. C.: "The Nutritive Significance of the Amino Acids," *Physiol. Rev.*, 18:109, 1938.

2 Daft, F. S., Robscheit-Robbins, F. S. and Whipple, G. H.: "Plasma Protein Given by Vein and Its Influence upon Body Metabolism," *J. Bio. Chem.*, 123:87, 1938.

3 Elman, R.: "Parenteral Replacement of Protein with the Amino-Acids of Hydrolyzed Casein," *Ann. Surg.*, 112:594, 1940.

4 Madden, S. C., Carter, J. R., Kattus, A. A., Miller, L. L. and Whipple, G. H.: "Ten Amino Acids Essential for Plasma Protein Production Effective Orally or Intravenously," *J. Exp. Med.*, 77:277, 1943.

5 Fink, R. M., Ennis, T., Kimball, C. P., Silberstein, H. E., Ball, W. F., Madden, S. C. and Whipple, G. H.: "Plasma Protein Metabolism-Normal and Associated with Shock," *J. Exp. Med.*, 80:455, 1944.

6 Cox, W. and Mueller, A.: "Serum Albumin Regeneration as Effected by Intravenously and Orally Administered Protein Hydrolysates," *J. Clin. Invest.*, 23:875, 1944.

7 Madden, S. C., Anderson, F. W., Donovan, J. C. and Whipple, G. H.: "Plasma Protein Production Influenced by Amino Acid Mixtures and Lack of Essential Amino Acids," *J. Exp. Med.*, 82:77, 1945.

8 Madden, S. C. and Whipple, G. H.: "Amino Acids in the Production of Plasma Protein and Nitrogen Balance," *Amer. J. Med. Sc.*, 211:149, 1946.

9 (a) Elman, R. and Wiener, D. O.: "Intravenous Alimentation with Special Reference to Protein (Amino-Acid) Metabolism," *J. Amer. Med. Ass.*, 112:796, 1939.
(b) Elman, R.: "Parenteral Alimentation in Surgery," *Paul B. Hoeber, Inc.*, New York and London, 1947.

10 Peters, J. P.: "Problems of Nitrogen Metabolism," *Federation Proc.*, 3:197, 1940.

11 Altshuler, S. S., Hensel, H. M. and Sahyun, M.: "Maintenance of Nitrogen Equilibrium of Amino Acids Administered Parenterally," *Amer. J. Med. Sc.*, 200:239, 1940.

12 Madden, S. C., Zeldis, L. J., Hengerer, A. D., Miller, L. L., Rowe, A. P., Turner, A. P. and Whipple, G. H.: "Plasma Protein," *J. Exp. Med.*, 73:727, 1941.

13 Clark, D. E., Brunschwig, A. and Corbin, N.: "Utilization of Parenterally Administered Casein Digest for Synthesis of Proteins," *Proc. Soc. Exper. Bio. and Med.*, 49:282, 1942.

14 Gardner, C. E. and Trent, J. C.: "Intravenous Amino Acid Adminis-

tration in Surgical Patients Using an Enzymatic Casein Digest," *Surg., Gyn., Obst.*, 75:657, 1942.

15 Altshuler, S. S., Hensel, H. M., Hecht, P. and Pursley, R.: "Maintenance of Nitrogen Equilibrium by Intravenous Administration of Amino Acids," *Arch. Int. Med.*, 70:749, 1942.

16 Madden, S. C., Woods, R. R., Shull, F. W. and Whipple, G. H.: "Amino Acid Mixtures Effective Parenterally for Long Continued Plasma Protein Production, Casein Digests Compared," *J. Exp. Med.*, 79:607, 1944.

17 Madden, S. C., Woods, R. R., Shull, F. W., Remington, J. H. and Whipple, G. H.: "Tolerance to Amino Acid Mixtures and Casein Digests Given Intravenously; Glutamic Acid Responsible for Reactions," *J. Exp. Med.*, 81:439, 1945.

18 (a) Farr, L. E., Emerson, K. Jr. and Putcher, P. H.: "The Comparative Nutritive Efficiency in Intravenous Amino Acids and Dietary Protein in Children with Nephrotic Syndrome," *J. Ped.*, 17:595, 1940.
(b) Farr, L. E.: "Intravenous Administration of Small Doses of Casein Hydrolysate to Nephrotic Children and Its Effect upon Nitrogen Balance and Plasma Amino Acid Level," *J. Ped.*, 16:679, 1940.

19 "Amigen," descriptive booklet prepared by Mead Johnson and Co., Evansville, Indiana, 1945.

20 (a) Sherman, Henry C.: "Chemistry of Food and Nutrition," 6th Edition, *The Macmillan Co.*, 1941.
(b) Bridges, Milton A. and Mattice, Marjorie R.: "Food and Beverage Analyses," *Lee and Febiger*, Philadelphia, 1942.

21 Folin, O.: "On Determination of Creatinine and Creatine in Urine," *J. Bio. Chem.*, 17:469, 1941.

22 VanSlyke, D. D.: "Gasometric Micro-Kjeldahl Determination of Nitrogen," *J. Bio. Chem.*, 71:235, 1927.

23 Gregersen, M. I.: "A Practical Method for the Determination of Blood Volume with the Dye T-1824. A Survey of Present Basis of the Dye Method and Its Clinical Applications," *J. Lab and Clin. Med.*, 29:1266, 1944.

24 Gutman, A., Moore, D., Gutman, E., McClellan, V. and Kabat, E.: "Fractionation of Serum Proteins in Hyperproteinemia with Special Reference to Multiple Myeloma," *J. Clin. Invest.*, 20:765, 1941.

25 Taylor, H. L., Erickson, L., Henschel, A. and Keys, A.: "The Effect of Bed Rest on the Blood Volume in Normal Young Men," *Amer. J. Physio.*, 144:227, 1945.

26 Keeton, R. W.: "Convalescence: A Study in the Physiological Recovery of Nitrogen Metabolism and Liver Function," *Ann. of Int. Med.*, 28: 521, 1948.

27 Peters, J. P.: "Problems of Nitrogen Metabolism," *Fed. Proc.*, 3:197, 1944.

28 (a) Elman, R.: "Intravenous Injection of Amino Acids in Regeneration of Serum Protein Following Severe Experimental Hemorrhage," *Proc. Soc. Exper. Bio. and Med.*, 36:867, 1937.
(b) Elman, R., Sachar, L. A., Horwitz, A. and Wolff, H.: "Regeneration of Serum Albumin with Hydrolyzed Protein in Chronic Hypoproteinemia Produced by Diet (An Experimental Study)," *Arch. Surg.*, 44: 1064, (June) 1942.

29 Lusk, G.: "The Physiological Effect of Undernutrition," *Physio. Rev.*, 1:523, 1921.

30 Strang, J. M., McClugage, H. B. and Evans, Frank A.: "Nitrogen Balance During Dietary Corrections of Obesity," *Amer. J. Med. Sc.*, 181:336, 1931.

31 Keeton, R. W. and Bone, D. D.: "Diets Low in Calories Containing Various Amounts of Protein," *Arch. Int. Med.*, 55:262, 1935.

32 Benditt, E. P., Woolridge, R. L. and Stepto, Robert: "The Dynamics of Protein Metabolism," *J. Lab. and Clin. Med.*, 33:269, 1948.

33 Hoffman, William S., Kozoll, Donald D., Mok, W. T., Meyer, Karl A. and Popper, Hans: "The Determination of the Nitrogen Balance Index of a New Lypholized Amino Acid Preparation in Protein-Deficient Patients," *J. Lab. and Clin. Med.*, 33:2800, 1948.

34 Cuthbertson, D. P.: "The Distribution of Nitrogen and Sulphur in the Urine During Conditions of Increased Catabolism," *Biochem. J.*, 25: 236, 1931.

35 Howard, J. E.: "Protein Metabolism During Convalescence After Trauma," *Arch. Surg.*, 50:163, 1945.
36 Albright, F., Parson, W. and Bloomberg, E.: "Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis: Results of Treatment with Testosterone Propionate," *J. Clin. Endo.*, 1:375, 1941.
37 (a) Kenyon, A. T., Knowlton, K., Lutwin, G., Munson, P. L., Johnston, C. D. and Koch, F. C.: "Comparison of Metabolic Effects of Testosterone Propionate with those of Chorionic Gonadotropin," *J. Clin. Endo.*, 2:685, 1942.
(b) Kenyon, A. T., Knowlton, K., Sandiford, I. and Fricker, L.: "The Metabolic Effects of Testosterone Propionate in Addison's Disease," *J. Clin. Endo.*, 3:131, 1943.
(c) Kenyon, A. T.: "The Effect of Testosterone Propionate on Nitrogen Electrolyte, Water and Energy Metabolism in Eunichoidism," *Endocrinology*, 23:135, 1938.
38 Kinsell, L. W., Hertz, S. and Reifenstein, E. C.: "The Effect of Testosterone Compounds Upon the Nitrogen Balance and Creatine Excretion in Patients with Thyrotoxicosis," *J. Clin. Invest.*, 23:880, 1944.
39 Daft, F. S.: "Physiological Aspects, Symposium on Folic Acid," *Ann. of New York Acad. Science*, 48:299, 1946.
40 Brunschwig, A., Clark, D. E. and Corbin, N.: "Postoperative Nitrogen Loss and Studies on Parenteral Nitrogen Nutrition by Means of Casein Digest," *Ann. Surg.*, 125:109, 1947.
41 Bassett, S. H., Woods, R. R., Shull, F. W. and Madden, S. C.: "Parenterally Administered Amino Acids as a Source of Protein in Man," *New England J. of Med.*, 230:106, 1944.
42 Schwimmer, D.: "Protein Metabolism Studies at Reduced Caloric and Water Intake," *Annual Protein Conference Bureau of Biological Research*, Rutgers Univ., New Brunswick, N. J., Feb. 6-7, 1948.
43 Cannon, P. R., Chase, W. E. and Wissler, R. W.: "The Relationship of the Protein-Reserves to Antibody-Production," *J. Immun.*, 47:133, 1943.

Report of the Committee on Chemotherapy and Antibiotics

The Use of PAS in Tuberculosis

In an endeavor to accumulate information as to the effectiveness of para-aminosalicylic acid in the various forms of tuberculosis, a total of 150 questionnaires was sent to the larger sanatoria in the United States by the Committee on Chemotherapy and Antibiotics of the American College of Chest Physicians during March 1949. A total of 110 replies was returned.

Only 25 institutions had used PAS or were willing to offer an opinion concerning its use. The total number of patients treated with this drug in this survey was 341. The preponderance of opinion indicated that 12 grams or more of PAS is the desirable daily dosage if it is tolerated in this amount, and that the duration of treatment should be between two and four months. The range of reported dosage generally was from about 5 grams to over 12 grams daily, and the desired duration of treatment was reported from less than two months to six months.

Of the 25 sanatoria reporting experience to some degree with PAS, 13 think that it is helpful in tuberculosis. Only two offered the opinion that it is definitely not helpful in tuberculosis, while 11 had formed no opinion as yet. The various types of tuberculosis in which PAS has been used and the totals of favorable impressions as to its use in those types are as follows: pulmonary 12, tracheobronchial 5, laryngitis 2, draining sinus 1, pleural effusion 2, empyema 1, genito-urinary 3, bones and joints 1, enteritis 1, and miliary 1.

Nineteen physicians among those answering the questionnaire had used PAS in combination with streptomycin. Six of these were of the opinion that it has a synergistic or additive effect, while 13 had come to no conclusion as yet.

To summarize briefly, it seems to be the feeling among the men with some experience with the drug that the optimum dose of PAS is 12 grams or more if it is tolerated in this amount, and that the duration of treatment should be from two to four months. PAS seems to have some usefulness in the chemotherapy of various types of tuberculosis, and appears to have some synergistic or additive effect when used in conjunction with streptomycin.

The Use of Streptomycin During Pregnancy

During the years that streptomycin has been used clinically in the treatment of tuberculosis, there has been a feeling of great

hesitancy on the part of many physicians to use this drug in pregnant women, due to the fear of possible severe ill-effects on the hearing and vestibular apparatus of the foetus. In view of this fact, it seemed very desirable to the committee to attempt to establish how well founded this fear may be and to determine the present attitude of chest physicians toward the use of streptomycin during pregnancy. So a questionnaire regarding the use of streptomycin in pregnant women was also sent to 150 institutions where tuberculosis is treated.

From the answers received the committee learned that 29 of the physicians questioned had used streptomycin in a total of 51 such patients. Of the physicians reporting, 11 preferred a daily dosage of 0.5 grams, 16 preferred 1.0 gram, and 2 thought that 2.0 grams daily to be the optimum dose. A majority felt that the optimum duration of treatment in such cases to be from 30 to 60 days. Four physicians preferred to treat the patients entirely as in non-pregnant cases. At the time the reports were received 46 babies had been delivered and no ill effects had been observed in any of them to date. Five had not yet been delivered at that time.

In summary, streptomycin when used during pregnancy seems to have no serious deleterious side-effects on the foetus. The preferred daily dosage among the physicians answering the questionnaire ranges from 0.5 to 1.0 gram, and the duration from 30 to 60 days.

In view of the above favorable reports, it would appear that streptomycin may be used in pregnant women with reasonable safety to the foetus, in doses of 0.5 to 1.0 gram daily, for periods of 30 to 60 days. Since it is of great importance that the present favorable impression be either confirmed or disproved, the Committee on Chemotherapy and Antibiotics would greatly appreciate receiving reports from other physicians who have had experience with streptomycin in such cases.

Urgoiti of La Coruna, Spain, has reported that one of the thiosemicarbazones, designated as TB-1, has shown promising results in experimental tuberculosis. The antituberculosis action of the thiosemicarbazonen was first announced by Domagk, Benisch, Mietzsch, and Schmidt in 1946. (Naturw., 1946, 10:315). In 1947 the first clinical trials were reported by Moncorps and Kalkhoff (Med. Klin., 1947, 42:812). In 1948 Arold in Weisbaden discussed clinical investigations in which the drug was found useful in tuberculous ulcers, intestinal tuberculosis, and in exudative lesions but not in tuberculous meningitis. He reported that the drug may be injurious to the kidneys, liver, and hematopoietic system.

Investigation of the thiocarbazones has started in the United States. A preliminary report of the action of one of these com-

pounds in experimental tuberculosis in mice was recently reported by Donovick and Bernstein (Am. Rev. Tuberc., 60:539, October 1949).

Tuberculosis physicians in the United States will await with interest results of further laboratory and clinical investigation of these compounds.

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Editorials

THE NEED FOR MORE INTELLIGENT USE OF STREPTOMYCIN IN MANAGEMENT OF PULMONARY TUBERCULOSIS

In January 1944, Schatz, Bugie and Waksman reported their discovery of streptomycin. Less than a year later, in the autumn of 1944, enough laboratory work and animal experiments had been done to justify the cautious use of the drug in humans suffering from miliary, meningeal or far advanced pulmonary tuberculosis. Shortly thereafter patients with a less hopeless prognosis were treated. Soon it became evident that streptomycin was a useful drug in the treatment of tuberculosis. Like other valuable drugs, streptomycin has its limitations as well as its assets and early clinical investigators of the drug were quick to point out that streptomycin was *not* a "cure all" for tuberculosis and that it was *not* a substitute for other proved procedures, such as bed rest and collapse therapy. It was early emphasized in regard to pulmonary tuberculosis that the best end-results would be obtained using streptomycin as an adjunct to other therapeutic measures.

It is now five years since streptomycin was first used in clinical tuberculosis. During this period a wealth of valuable information has been added to our knowledge of the drug to guide physicians in its intelligent use. In spite of the vast amount of knowledge accumulated and the numerous splendid papers written, there is still abundant evidence to indicate that use of streptomycin is too often abused. In many instances the life of the patient may be

jeopardized by injudicious use of the drug in the over-all management of the case.

The occurrence of streptomycin-resistant tubercle bacilli is undoubtedly the chief stumbling block in the use of the drug and this factor must constantly be borne in mind by the physician treating tuberculosis. Since present evidence clearly indicates that streptomycin-resistant organisms occur in a majority of patients who have received streptomycin for a period of two to three months or longer it is imperative that the optimum time for the use of the drug be carefully determined in each case. Procedures such as pneumothorax and thoracoplasty and particularly pulmonary resection are most often effective when timed properly in relation to the administration of the drug. The advent of dihydrostreptomycin which lessens the occurrence and severity of toxic side effects, has not changed the picture as regards the phenomenon of drug-resistance.

During the past year several investigators have reported that the appearance of streptomycin-resistant organisms can be considerably delayed in a majority of the patients under study by the administration of para-aminosalicylic acid (PAS) in combination with streptomycin. These preliminary reports are encouraging and if they are sustained by further investigation, it may be hoped that our treatment of certain cases can be modified and improved by such combined therapy. The work of Tempel and Dye regarding intermittent dosage schedules of streptomycin as reported in this issue of "Diseases of the Chest" is also encouraging.

In view of the fact that within a short period of five years streptomycin has become universally accepted as an invaluable aid in the treatment of the various forms of tuberculosis, it seems appropriate at this time to comment on the tremendous achievement of those who have had a share in developing the present knowledge of this drug. Surely this accomplishment is a monument to all the groups, organizations and drug firms, who have worked together in such close and active cooperation, pooling their experience, resources and results to accumulate so much information in such a short time. This experience in the clinical evaluation of streptomycin should serve as a splendid example of what can be accomplished by cooperative effort. Surely this same fine spirit of cooperation, if continued will insure a rapid and thorough clinical evaluation of any new and promising antituberculosis agents which may be discovered in the future.

KARL H. PFUETZE, M.D., F.C.C.P., Chairman
Committee on Chemotherapy and Antibiotics.

THE NEED FOR FURTHER INVESTIGATION AND RESEARCH IN CHEMOTHERAPY AND ANTIBIOTICS

Perhaps it is not an exaggeration to say that in no other field of medicine has the development of antibiotics had so far reaching an effect as in diseases of the chest. It is not only that methods of therapy and approach to the various pathological conditions have been radically changed, for that can be said of almost every other field of medicine. The emphasis lies in the fact that conditions considered previously as untreatable are now being attacked directly, and that as this occurs, a number of conditions, hitherto unknown or unrecognized, are assuming a position of major importance. In this latter category may be placed that group of pneumonic conditions variously classified as atypical pneumonias or virus infections, while in the former are miliary tuberculosis and chronic bronchiectasis of wide distribution.

Through the early sulfa and penicillin days, pneumococcus pneumonia was the chief area of usefulness for these therapeutic agents. It was not long before clinical investigation, following the work of Castex, indicated that penicillin at least, could be used to attack many chronic and acute infections of the bronchi directly by the aerosol method. This not only opened up a new method of approach in treatment, but through the work of Barach, Olsen, Segal and others showed that conditions such as sinus infection and bronchiectasis might yield to this medical treatment.

During all this period, one of the major problems—that of tuberculosis—was in nowise affected. The discovery of another antibiotic, streptomycin, brought the striking and now well-established change in the treatment of this disease. Other new agents have continued to be discovered; they have taken their place in the handling of various conditions, or have been found ineffective for a variety of reasons.

Thus, we find PAS becoming an established medication in tuberculosis, while aureomycin and chloromycetin are promising to be major factors in the control of virus and certain bacterial infections. What is perhaps more surprising, is our very lack of astonishment at the announcement that a new antibiotic has been developed. We have come to expect these almost as regularly as changes in the weather.

These medications, which in one sense have made it so much easier for the chest specialist to treat disease, have, on the other hand, presented him with additional problems that cannot be evaded. When pneumonia or tuberculosis was being treated symptomatically by rest and by minor medicaments, it did not matter too much whether the attending physician had a clear or a hazy

concept of the type of pathology responsible for the disease. The result was not varied in the majority of cases by his knowledge or the lack of it. Today, when he is using antibiotic agents which may attack the disease directly, he must know not only the causative organisms and what their sensitivities may be, but the very nature of the pathological process. This latter information may determine the mode of administration and the necessary adjuncts to accomplish a cure. For example, in acute bronchial infection, an antibiotic may be effective which reaches the disease through the bloodstream. In long standing chronic infection of the bronchi, such an approach may be valueless because of the barriers established between the infection and the blood supply, and the more direct approach of aerosol may be indicated. The limitations of streptomycin in cavitary tuberculosis is another such example. Here the knowledge of this pathology with the inability of streptomycin to penetrate the cavity wall may indicate collapse or surgery as the major portion of the treatment, and the physician is not lulled into a sense of false security by improvement in the early months of treatment.

There is another aspect to this same subject, no less important but perhaps less obvious. This is the necessity of understanding the physiological changes which are occurring and the need for correcting these in addition to the elimination of the infection. This circumstance may be found in a virus pneumonia where the elimination of the infection may find bronchi and bronchioli edematous and filled with secretion, while interalveolar changes handicap both gas exchange and pulmonary circulation. The necessity of correcting these difficulties and of supporting respiration and circulation until a normal status has been reached is no less important than the administration of the newest and most expensive of the antibiotics.

In fact, it is fair to say that these short cuts in treatment, the antibiotics whose value cannot be overemphasized, have placed a greater premium on the art and skill of the physician. It was easier when large numbers of patients were dying of diseases which were enigmas to medical science. If there are successful methods of attack for some of these conditions, as indeed there are, it becomes of prime importance to classify, segregate and catalog them in pathological and physiological reactions and their response to treatment, and to be able to do so when confronted by a clinical picture in an ailing patient. A pneumonic process, even if it does respond clinically to antibiotics, may mask a tumor and valuable time is lost during the period of acceptance of congratulations and explaining why the complete disappearance of the pulmonary shadow is taking so long. The tuberculin test and the sputum

examination are likely to be overlooked but never before have they been so important. The one or the other may serve as a definite indication of what should or should not be done.

In this connection, the responsibility of the chest specialist is ever increasing now, when many physicians, without the advantage of training in this specialty, are being called upon to use these antibiotics. This is as it should be, since under our system, the family doctor is the man who sees and treats most illness. But the specialist must investigate and study and collect his observations and opinions. And he must impart through formal courses, meetings, and informal discussions all the information which he may possess to whatever medical men may be interested. This is not an elective procedure, it is his duty and his responsibility to ensure that these miraculous medications are used to the greatest benefit of the general public.

It is likewise important that investigation and research along these lines be continued and increased. The field is so great that no man's experience can cover all aspects of the voluminous studies that are necessary to determine how and when these antibiotics shall be used. These constant studies must be correlated and evaluated and the digest passed on so that all may know what has been accomplished and what further investigation is necessary. This is a task which has been allotted to the Committee on Chemotherapy and Antibiotics of the Council on Management and Treatment of Diseases of the Chest. It is an awesome task not to be taken lightly. Too often have preliminary results been contradicted by long term observation. And too frequently has an obvious fact been shown by further research to be a fiction instead. Yet this task must be done and in keeping with the over-all nature of the field of diseases of the chest, must be correlated with the work of the other committees of this Council, those on Surgery, Collapse and Physiologic Treatment. This information collected and digested is issued from time to time as a report by the committee in question. These reports are not intended to represent a statement of authority nor yet to delineate the only accepted methods of treatment by which the therapy of any physician might be measured. They are rather intended to represent a digest of experience and the current opinion on any drug or treatment. Thus they can be used as a source of information. This special issue of "Diseases of the Chest" represents another function of this Committee. Under the leadership of Dr. Karl Pfuetze, the Committee on Chemotherapy and Antibiotics has compiled and arranged this issue containing recent and authorative information on antibiotics and chemotherapeutic agents. These being original contributions are not published as a

Committee Report but represent the experience and informations of the authors alone.

This is another type of Committee activity in addition to the regular digests of opinion. By such activity it is hoped that the lag between investigation and clinical practice may be shortened so that medical advance as represented by such things as antibiotics may improve the treatment of diseases of the chest as rapidly as is consistent with good scientific experience.

EDWIN R. LEVINE, M.D., F.C.C.P., Chairman
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THE GLORY OF TWENTIETH CENTURY MEDICINE

The last 25 years of the 19th century was the most productive era in the history of medicine from the standpoint of determining etiology of human and animal diseases. After Hansen announced the discovery of the bacillus of leprosy in 1874, one organism after another was found to be specific for certain diseases, such as gonorrhea, typhoid fever, anthrax, tuberculosis, lobar pneumonia, glanders, diphtheria, tetanus, brucellosis, cerebrospinal meningitis, bubonic plague, etc., etc. The epoch-making discoveries in parasitology and bacteriology was one of the chief glories of medicine of the 19th century.

Aside from the production of antitoxin for diphtheria and tetanus, little was accomplished in the 19th century by way of treating the diseases whose causes had become known. In the early part of the 20th century, much time and effort were expended searching for specific therapy for the bacterial diseases. As the fourth decade of the 20th century opened, no adequate specific therapy had been found for a sizable number of the most destructive diseases that attack the chest. One discouragement after another had caused many workers to almost lose hope.

When Domagk discovered and reported in 1935 that prontosil has an antibacterial action on hemolytic infection in mice and it was soon observed that infections caused by the gonococcus and meningococcus yielded to this drug, there was a revival of interest in chemotherapy for all of the bacterial diseases.

From this beginning, various sulfonamide compounds were found to be so effective in controlling certain bacterial diseases that they were promptly referred to as "miracle drugs." While these preparations were at the height of deserved popularity, antibiotic substances were introduced for disease control. Penicillin was soon designated the "wonder drug." Only five years ago, the isolation of streptomycin was announced and in 1948 aureomycin was introduced.

Penicillin was found especially helpful in controlling infections with Gram-positive organisms. Streptomycin controlled some of the Gram-negative bacteria which were resistant to penicillin. There remained a number of organisms which were unaffected by penicillin and streptomycin which are controlled by aureomycin.

Practically all of the organisms that result in suppurative conditions of the chest, such as pulmonary abscess and empyema, are sensitive to one or more of these antibiotics. In fact, a synergistic relation has been demonstrated to exist between aureomycin and polymyxin or penicillin *in vitro* and between aureomycin and penicillin *in vivo*.

Most of the organisms which have been responsible for the pneumonias, such as pneumococci and streptococci, are now treated successfully by one or more of these preparations. Even cases of primary atypical pneumonia have been reported to respond to aureomycin. Even the bacillus of Friedlander apparently is sensitive to this antibiotic. Diseases such as brucellosis and tularemia which occasionally attack the lungs and pleura respond to one or more of these preparations.

Several of the rickettsial infections which may produce pneumonitis, such as Q fever, Rocky Mountain spotted fever and typhus fever, respond to aureomycin.

Since the chest yielded up most of its secrets to the surgeon, infections constituted an important hazard in chest surgery. The use of antibiotics has largely removed the dangers of such infections.

Hope was revived in chemotherapy for tuberculosis when a sulfone preparation known as promin was found to suppress experimental tuberculosis in 1940, and again when the bacteriostatic effect of para-aminosalicylic acid (PAS) was discovered in 1943.

Streptomycin was the first antibiotic to yield impressive results on tuberculosis in both animals and humans, with the first report on experimental tuberculosis in December, 1944 and the first on clinical tuberculosis in September, 1945.

Dihydrostreptomycin was announced in 1946. During the present year neomycin was introduced, but has not been released for clinical use except for carefully conducted studies. Although the sulfones, PAS and the antibiotics, including streptomycin and dihydrostreptomycin, have not proved to be bactericidal, they do possess bacteriostatic properties which are proving of value in the treatment of tuberculosis. However, they must be considered only as adjuncts to the usual therapeutic procedures. To date, streptomycin has proved to be the most promising drug in the treatment of tuberculosis. However, it possesses serious limitations such as the resistance which tubercle bacilli develop to it and its

toxic qualities. So far, these have been overcome only in part. Neomycin in the laboratory has proved more active against both pathogenic and saphrocytic acid-fast organisms. It is as active against the streptomycin-sensitive as against the streptomycin-resistant tubercle bacilli. Apparently organisms do not develop resistance to it as they do to streptomycin.

Never before has so much interest been manifested by so many physicians or as much money spent in such a short period of time on any treatment of tuberculosis as on the antibiotics during the past five years. A gigantic and well ordered study on the effects of streptomycin, dihydrostreptomycin and PAS has been conducted with the greatest of care by the United States Veterans Administration in cooperation with the Army and the Navy in the treatment of 7,000 tuberculous persons to the benefit of the patients and to the accruement of knowledge. Extensive studies have also been conducted by the Therapy Committee of the American Trudeau Society, the Division of Tuberculosis of the United States Public Health Service, the staffs of hospitals and sanatoriums and private physicians. While a few facts have been established, much remains to be learned.

The papers which appear in this issue of "Diseases of the Chest" clearly state the facts that have been established, indicate work in progress and point to desired goals. Most of the authors were invited to prepare manuscripts for this special issue. All deserve much credit for the expenditure of so much time and effort to make their large store of knowledge available to the readers of this journal throughout the world.

Progress is being made with such rapidity, particularly in the production of new antibiotics that one may momentarily expect better preparations or more efficacious ones to be announced.

It is probable that the chemotherapeutic agents and the antibiotics that have been developed within the past dozen years, and others that may soon be available, will add several years to the span of human life on the earth. Moreover, it is likely that they will contribute to comfort, greater working capacity and efficiency among older people by promptly destroying the diseases in earlier life which result in impairment of function of vital parts when old age is attained. It already appears safe to predict that these epoch-making discoveries in therapy will constitute the chief glory of 20th century medicine.

The Editorial Board of "Diseases of the Chest" is grateful to the Committee on Chemotherapy and Antibiotics and to the Council on Management and Treatment of Diseases of the Chest for this splendid issue of the journal.

J. ARTHUR MYERS, M.D.

First International Congress on Diseases of the Chest

The First International Congress on Diseases of the Chest will be held at the Forlanini Institute, Rome, Italy, September 17 through 20, 1950. The Congress will be sponsored by the Council on International Affairs of the College in cooperation with the Forlanini Institute. A scientific program covering all phases of diseases of the chest will be presented, as well as an x-ray conference, a motion picture session, and other functions. Professors Attilio Omodei Zorini and Eugenio Morelli, Directors of the Forlanini Institute, will serve as co-chairmen of the committee on arrangements for the Congress. Physicians interested in presenting papers at the Congress are invited to submit titles and abstracts of their material to the program committee for consideration. Please send the information to the Executive Offices of the College, 500 North Dearborn Street, Chicago 10, Illinois.

College Chapter News

CUBAN CHAPTER

A Board of Past Presidents of the Cuban Chapter was organized at the time of a business meeting of the Board of Officers of the chapter held at the Curie Hospital, Havana, on October 31st. The Board is composed of Dr. Gustavo Aldereguia, Chairman; Professor Alfredo Antonetti, Dr. Teodosio Valledor and Dr. Octavio Rivero, Governors of the College for Cuba. Other officers of the chapter attending the meeting were Dr. Antonio Navarrete, Regent of the College for Cuba; Dr. Francisco J. Menendez, President of the Cuban Chapter; Dr. R. Sanchez Acosta, Vice-President and Dr. Carlos Barroso, Secretary.

On November 9 the Cuban Chapter held a meeting at the Academy of Sciences in Havana at which Professor Dante Decanini of Monterrey, Mexico, and Professor Alberto Chattas of Cordoba, Argentina, were guest speakers. The following scientific program was presented:

"Extrapleural Oleothorax,"
Prof. Dante Decanini, Monterrey, Mexico.
"BCG Vaccination,"
Prof. Alberto Chattas, Cordoba, Argentina.
"Bronchogenic Carcinoma,"
Drs. A. Rodriguez Diaz and V. Anido, Havana, Cuba.
"Cysts of the Lung,"
Drs. R. Gomez and Laura Farinas.

ILLINOIS CHAPTER

A joint meeting was held by the Illinois Chapter of the College and the Chicago Roentgen Society at the University Club, Chicago, on Thursday, November 10th. Dinner was served at 6:30 p. m. and was followed by a scientific program. The following program was presented:

"Interesting Case Reports,"
C. Giles Cailleteau, M.D. and Marvin Rassell, M.D., Hines, Illinois.
"The Adult Asymptomatic Chest,"
George M. Landau, M.D., Chicago, Illinois.
"Bronchography in Infants,"
Albert H. Andrews Jr., M.D., F.C.C.P., Chicago, Illinois.

KENTUCKY CHAPTER

The organizational meeting of the Kentucky Chapter of the College was held at Owensboro, Kentucky, on Thursday, October 6th, at the time of the annual meeting of the Kentucky State Medical Association. Dr. Paul A. Turner, Louisville, was elected President of the new chapter; Dr. T. Ashby Woodson, Louisville, was elected Vice-President; and Dr. Hugh L. Houston, Murray, was elected Secretary-Treasurer. Dr. Richard H. Overholt, Brookline, Massachusetts, Past-President and Chairman of the Council on Pan American Affairs of the College, presented a paper at the meeting of the Kentucky State Medical Association and attended the meeting of the new chapter.

The members of the College in Kentucky who were present at the meeting applied for a charter for the Kentucky Chapter which has been submitted to the Board of Regents of the College. The application for a charter was signed by the following College members: Leslie C. Dodson, M.D., Owensboro; John B. Floyd, M.D., Richmond; Rudolph E. Gernert, M.D., Louisville; John S. Harter, M.D., Louisville; Hugh L. Houston, M.D., Murray; Carl C. Howard, M.D., Glasgow; Boyce E. Jones, M.D., Waverly Hills; R. O. Joplin, M.D., Louisville; John B. McHugh, M.D., Outwood; Heinz Oppenheim, M.D., Outwood; Hugo Polderman, M.D., Waverly Hills; J. Frank Stewart, M.D., Waverly Hills; Lawrence A. Taugher, M.D., Louisville; Lawrence O. Toomey, M.D., Bowling Green; Paul H. Turner, M.D., Louisville; T. Ashby Woodson, M.D., Louisville.

MICHIGAN CHAPTER

The Michigan Chapter of the College held a meeting at the Detroit Tuberculosis Sanatorium on November 9th. Dinner was served at 6:30 which was followed by a talk given by Dr. Carl Birkelo, Radiologist at Herman Kiefer Hospital, Detroit, on the subject of "Diagnosis of Diseases of the Chest."

SOUTHERN CHAPTER

At the annual meeting of the Southern Chapter of the College, held in Cincinnati on November 13 and 14, the following officers were elected for the coming year:

David H. Waterman, M.D., Knoxville, Tennessee, President.
M. Jay Flipse, M.D., Miami, Florida, First Vice-President.
Hollis E. Johnson, M.D., Nashville, Tennessee, Second Vice-President.
George R. Hodell, M.D., Houston, Texas, Secretary-Treasurer.

WISCONSIN CHAPTER

At the annual meeting of the Wisconsin Chapter held in Milwaukee on October 2, the following officers were elected for the ensuing year:

Carl O. Schaefer, M.D., Racine, President.
John P. Fetherston, M.D., Milwaukee, Vice-President.
Leon H. Hirsh, M.D., Milwaukee, Secretary-Treasurer.

Dr. Leon Hirsh reported that the Milwaukee Metropolitan Section of the Wisconsin Chapter met at the Medford Hotel in Milwaukee on Friday, November 25, 1949. Doctors Timothy R. Murphy and Armin R. Baier spoke on "Pulmonary Function." The presentation was followed by a round table discussion.

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W. N. TORRE, M.D., Resident Clinician **ALLEN B. LILIENTHAL, M.D., Clinician**

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